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Original Research

Dihydrotestosterone Remains Within Normal Range in Men Under Long Lasting Testosterone Therapy (TTh)

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ABSTRACT

The major goal of androgen therapy is to achieve testosterone levels as close to physiological concentrations as possible. For some androgen-dependent functions, testosterone is a pro-hormone, peripherally converted to 5a-dihydrotes-tosterone (DHT) and 17b-oestradiol of which the levels preferably should also be within their normal physiological ranges. In this study, the resulting plasma DHT levels in 122 hypogonadal men treated with a novel testosterone treatment modality: parenteral long-acting testosterone undecanoate (Nebido), were investigated. Following the treatment, there were no abnormally high/low plasma DHT levels; levels varied between 86 and 511 ng l)1 (normal range:40-575 ng l). In conclusion, treatment with testosterone undecanoate generates physiological levels of DHT. Prostate safety parameters did not undergo changes.

Keywords: Testosterone therapy; Dihydrotestosterone (DHT)-Drug profile; safety; Testosterone undecanoate

Introduction

5a-Dihydrotestosterone (DHT), the most potent natural androgen, is formed exclusively through 5a-reduction of testosterone (T) by the enzyme 5a-reductase. This enzyme has two forms produced by distinct, homologous genes, with 5a-reductase type 1 expressed in liver, skin and brain, whereas 5a-reductase type 2 is characteristically expressed strongly in the peripheric prostatic zone with lower levels in skin and liver[1,2]. Circulating DHT levels are approximately 10% of the blood T levels, mostly arising from nongonadal tissues that express 5a-reduc-tase type 2. The testis expresses type 1 5a-reductase[3], but at relatively low levels, so that the testis secretes minimal quantities of DHT into the bloodstream. From this it follows that exogenous testosterone, in the same way as endogenous testosterone, will be subjected to conversion to dihydrotestosterone in peripheral tissues via the two enzymes 5a-reductase type 1 and 2.

Indeed, administration of testosterone preparations leads to increases of not only testosterone but also DHT. There are variations in the amount of DHT generated with each testosterone treatment modal-it. Transdermal testosterone preparations generate higher plasma levels of DHT than

parenterally administered testosterone[4], likely because of the high concentrations of type 1 5a-reduc-tase in the skin. The major goal of androgen treatment is to achieve testosterone levels as close to physiological concentrations as possible. For some androgen-dependent functions, testosterone is a pro-hormone, peripherally converted to DHT and 17b-oestradiol of which the levels preferably should be within their normal physiological ranges[5]. Therefore, we tested the resulting plasma DHT levels in hypogonadal men treated with a novel testosterone treatment modality: parenteral long-acting testosterone undecanoate (Nebido; Bayer Schering Pharma, Berlin, Germany).

Patients and Methods

A total of 122 patients receiving testosterone undecanoate (TU) injections i.m. were monitored for 1 year. Their ages were between 55 and 74 years (median 64 years). They had sought primarily consultation for sexual dysfunction. Many suffered also from metabolic syndrome. If their plasma testosterone levels were below the lower limit of normal (normal range: 3.8–8.6 ng ml−1), they were eligible for testosterone treatment. Contra-indications were past or present prostate carcinoma, elevated plasma levels of prostate-specific antigen (PSA) (>4μg l−1), severe disease such as terminal cardiac disease, severe diabetes mellitus, serious renal and liver disease which might be aggravated by T administration. These patients followed the treatment protocol developed for TU: first injection on day 1, next after 6 weeks and subsequently every 12 weeks. Before treatment, five patients had elevated plasma DHT levels of over 600 ng l−1 (DHT normal range: 40–575 ng l−1, measured with Architect Abbott; Abbott, Wiesbaden, Germany). Three men were started on 5α-reductase inhibitor for presumed prostate safety **(Figure 1)**, whereas the other two were not willing to take this drug. All patients underwent blood sampling for the measurement of total testosterone, DHT and PSA before treatment and after week 6, week 18 and subsequently every 12 weeks while receiving therapy for a total duration of 12 months. Plasma total testosterone and dihydrotestosterone were measured with immuno-assays (Architect, Abbott). For DHT, the intra- and intraassay coefficients of variation were 9.1% and 6.6% respectively. The intra- and inter-assay coefficients of variation were 4.0% and 5.6% for testosterone.

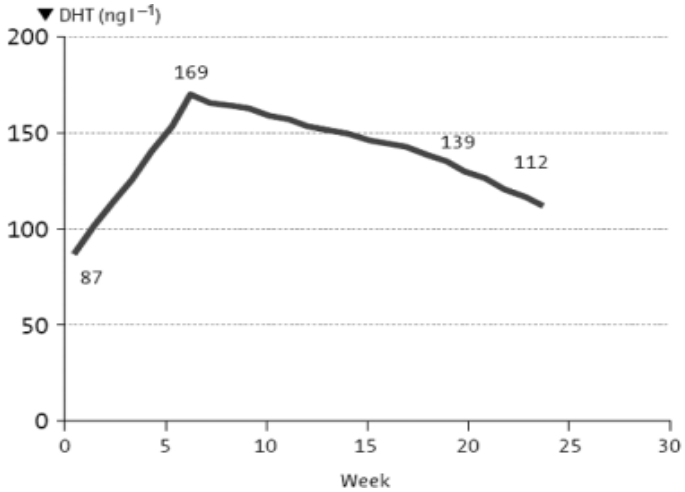

Figure 1: Mean dihydrotestosterone (DHT) serum concentration in 122 hypogonadal patients after four i.m. administrations of Nebido® DHT (ng l−1): max=573, min=36

Prostate safety parameters were measurement of PSA, digital rectal examination (DRE) and transrectal ultrasound (TRUS) and the International Prostate Symptom Score (IPSS). The data were collected from data obtained during standard medical care in the treatment of men with late onset hypogonadism.

Statistical analysis

Anova was conducted for repeated measurements. Data were analyzed by descriptive statistical methods using sas version 6.12 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1. clarifying the recently established recommended dosage schedule of TU was followed. Plasma levels of total testosterone rose significantly but remained within the normal physiological range in all subjects over the whole treatment period between 4.8 ± 1.5 and 8.0 ng ml−1 (normal range: 3.8–8.6 ng ml−1). Initially, a small but significant rise of DHT levels was found (P = 0.05), but after 12 months of administration of TU, DHT declined slightly but significantly (P < 0.05). Plasma DHT levels in these patients showed no abnormally high/low levels and varied between 86 and 511 ng l−1 (normal range: 40–575 ng l−1). The two patients with elevated DHT who had refused therapy with 5α-reductase inhibitor for prostate safety issue, surprisingly, showed normalization of DHT level under therapy with TU. There was a slight, nonsignificant increase in prostate volume: 38.1 ± 1.1 to 40.0 ± 1.4 ml, with a change in the volume of the transitional zone: 14.0 ± 6.1 ml to 15.4 ± 1.2 ml (nonsignificant). There were no abnormalities on ultrasound investigation. There was a slight improvement in IPSS from 15.0 ± 1.0 ml to 13.7 ± 1.1 ml. PSA values were at baseline 1.08 ± 0.25 ng ml−1 and rose to 1.15 ± 0.21 ng ml−1 (nonsignificant). There were no abnormal findings with DRE. Comparison between TU and TE injections showed no significant alterations **(Figure 2)**.

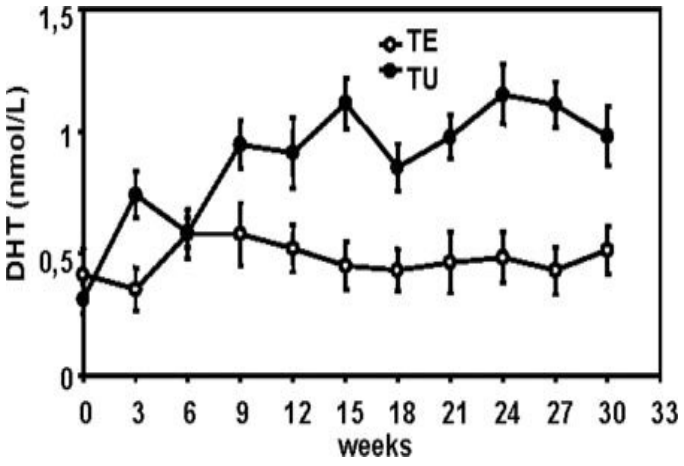

Figure 2: Serum DHT levels (mean SEM) during the first 30 wk of therapy. Blood samples were collected every 3 weeks

Discussion

Our results show convincingly that treatment with long acting parenteral testosterone undecanoate (Nebido), following a recently established regimen of injections, not only generates plasma T levels in the physiological range but also that the conversion product of T, DHT, remains in the physiological range, therewith fulfilling criteria for adequate treatment with T[5]. Studies with TU have shown that plasma DHT rises in parallel

with plasma T upon its administration[6]. and therefore this result is unexpected. As DHT is implicated in the development of benign prostatic hyperplasia (BPH) and prostate cancer, high DHT blood levels have traditionally been regarded as undesirable. But clinical observations, be it in small sample sizes and over limited periods of time, of supraphysiological DHT levels following androgen treatment are reassuring. Studies with scrotal testosterone patches providing a long-term outcome with high DHT blood levels over a period of several years, do not indicate any risk of prostatic hyperplasia or cancer, although they involve only a small number of patients[7]. Furthermore, three DHT gel studies did not report any increase in PSA levels, prostate volume or symptoms[8-10]. However, these are short-term studies over 3 or 6 months. In one study, even a 15% decrease of prostate volume was detected[8] and this is due to the following mechanism: DHT suppresses LH and FSH levels, resulting in lower endogenous T production which in turn leads to diminished aromatization of testosterone to estradiol.

Estradiol has been reported to be involved in the development of BPH[11]. Further, the androgen physiological mechanisms of the prostate are geared to maximize androgen effects, first by its high density of T receptors and second by its high degree of conversion of T to DHT[12], resulting in higher intraprostatic DHT levels than serum DHT levels and higher levels of intraprostatic DHT than levels of intraprostatic T. This could potentially explain why an elevation of peripheral DHT levels no impact on the prostate itself has, also apparent from studies that used DHT itself for androgen treatment which found no effect on the prostate[8-10]. In elderly hypogonadal men receiving testosterone treatment, intraprostatic testosterone and DHT do not rise significantly[13] and this could also explain why normalization of testosterone levels in hypogonadal men a significant impact on circulating DHT levels does not have of which the prostate is a source.

All the above are short-term studies with limited participants included in the studies, so the conclusions to prostate safety of chronically elevated plasma DHT levels must be regarded as preliminary. It has been estimated that a study to determine whether T treatment of men with late onset hypogonadism induces prostate cancer would need to include 6000 elderly hypogonadal men randomly assigned to testosterone or placebo for 6 years to determine whether T treatment increases the risk of prostate cancer by 30%[14]. It is therefore very doubtful whether such a study will be conducted in the short term and that a definitive answer will be forthcoming within the next 10-20 years. With this situation, the normal DHT levels generated with the administration of TU are reassuring **(Figure 3)**.

A surprising finding was the normalization of plasma DHT levels in the two men with elevated DHT levels before the administration of TU **(Figure 3)**. It has been hypothesized that DHT may provide an amplification mechanism for testosterone, which could be a beneficial adaptation in men with low circulating testosterone.

Upon normalization of testosterone levels, this amplification to DHT would no longer be needed[15,16]. So, there may be a reciprocal inverse relationship between 5a-reductase activity and plasma testosterone levels, thus protecting the organism from androgen deficiency if plasma testosterone levels are low **(Figure 4)**.

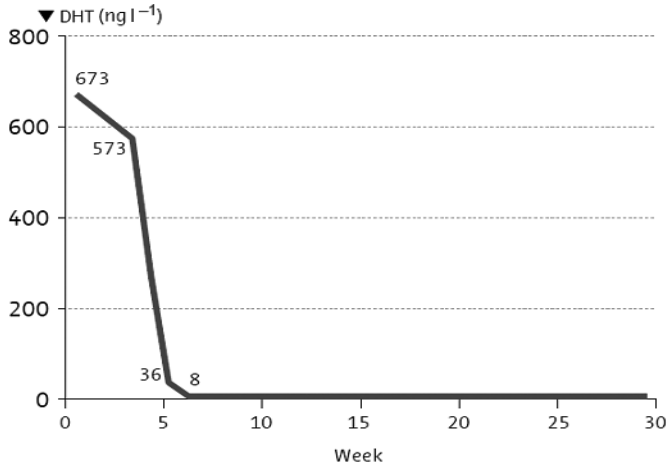

Figure 3: Dihydrotestosterone (DHT) levels in three patients with primary elevated DHT who received three i.m. administrations of Nebido in combination with 5a-reductase inhibitor Dutasteride.

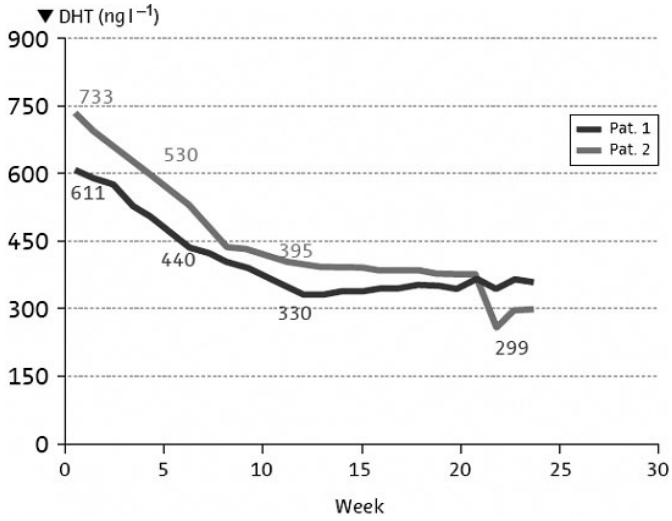

Figure 4: Two control patients with higher dihydrotestosterone (DHT) level at the baseline, who refused to take Dutasteride, show normalized DHT values under Nebido i.m. administration.

For profound knowledge and reading on this topic, multiple research results are available[17-24].

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