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Pharmacokinetics of testosterone cream applied to scrotal skin

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SUMMARY

Scrotal skin is thin and has high steroid permeability, but the pharmacokinetics of testosterone via the scrotal skin route has not been studied in detail. The aim of this study was to define the pharmacokinetics of testosterone delivered via the scrotal skin route. The study was a single-center, three-phase cross-over pharmacokinetic study of three single doses (12.5, 25, 50 mg) of testosterone cream administered in random sequence on different days with at least 2 days between doses to healthy eugonadal volunteers with endogenous testosterone suppressed by administration of nandrolone decanoate. Serum testosterone, DHT and estradiol concentrations were measured by liquid chromatograpy, mass spectrometry in extracts of serum taken before and for 16 h after administration of each of the three doses of testosterone cream to the scrotal skin. Testosterone administration onto the scrotal skin produced a swift (peak 1.9–2.8 h), dose-dependent ($p < 0.0001$) increase in serum testosterone with the 25 mg dose maintaining physiological levels for 16 h. Serum DHT displayed a time- ($p < 0.0001$), but not dose-dependent, increase in concentration reaching a peak concentration of 1.2 ng/mL (4.1 nM) at 4.9 h which was delayed by 2 h after peak serum testosterone. There were no significant changes in serum estradiol over time after testosterone administration. We conclude that testosterone administration to scrotal skin is well tolerated and produces dose-dependent peak serum testosterone concentration with a much lower dose relative to the non-scrotal transdermal route.

INTRODUCTION

Since the first clinical use of testosterone in 1937 (Hamilton, 1937), two years after its discovery as the principal mammalian androgen (David *et al.*, 1935), the need to overcome its distinctive pharmacological limitations of low oral bioavailability and short circulating half-life necessitated development of non-oral depot delivery systems (Handelsman, 2015). After eight decades in clinical use, the sole unequivocal indication for testosterone treatment is for replacement therapy in men with pathological hypogonadism, comprising organic disorders of the hypothalamus, pituitary or testes. These conditions require lifelong treatment as the underlying incurable reproductive disorders render the reproductive system unable to maintain physiological secretion of testosterone. Consequently, long-term compliance requires a convenient, minimally intrusive delivery system to facilitate continuity of treatment.

Currently, testosterone is mainly administered via oral, implantable, injectable or transdermal products (Handelsman, 2015). The single oral form is testosterone undecanoate in oil-filled capsule which facilitates absorption via intestinal lymphatics, avoiding hepatic and gut wall first-pass metabolism; however, the capsules must be taken 2–3 times daily with a fatty meal to be absorbed (Bagchus *et al.*, 2003). Implantable testosterone has favorable long-term (6 month) depot properties (Kelleher *et al.*, 2004), but insertion requires minor surgery which may cause discomfort and pellets may extrude (Handelsman *et al.*, 1997). Injectable products, testosterone esterified to fatty acids formulated in a vegetable oil vehicle, have been the affordable basis of testosterone replacement therapy since the 1950s (Junkman, 1957). However, they require potentially painful deep intramuscular injections (Sartorius *et al.*, 2010) and create highly fluctuating circulating levels with supra-physiological peaks alternating with low troughs that produce corresponding roller-coaster effects on mood (Jockenhovel *et al.*, 2009) and risk of erythrocytosis (Jockenhovel *et al.*, 1997).

Transdermal delivery of testosterone was first reported in the late 1980s (Findlay *et al.*, 1987). Transdermal absorption depends on testosterone forming a local depot in the stratum

corneum, the dead skin cell layer which limits permeability of small molecules through the skin, to allow for prolonged testosterone delivery (Barry, 1983). The first transdermal testosterone product, an adhesive scrotal patch (Findlay *et al.*, 1987; Behre *et al.*, 1999), was discontinued because of poor acceptability arising from the need for scrotal shaving, dermal irritation and poor adhesion when wet and elevated circulating DHT. Subsequently, non-scrotal patches were developed for application to truncal skin (Meikle *et al.*, 1996; Arver *et al.*, 1997), but they feature a generic limitation of application site irritation (as a result of necessary inclusion of absorption enhancers) leading to a high rate of skin reactions (Jordan *et al.*, 1998) including even severe burn-like skin reactions (Bennett, 1998). Transdermal testosterone gels are intended for application to truncal but not genital skin and feature low rates of dermal irritation (Handelsman, 2012), but risk topical transfer to women (de Ronde, 2009) and children (Martinez-Pajares *et al.*, 2012) in intimate contact with the patient. Yet, scrotal skin is advantageous for transdermal testosterone delivery as it has the thinnest stratum corneum (Smith *et al.*, 1961; Ya-Xian *et al.*, 1999), high steroid permeability (Wester & Maibach, 1989) many times greater than non-scrotal skin (Lin *et al.*, 1999), and minimizes the risk of passive topical transfer to others. The present dose ranging study aimed to determine the pharmacokinetics of testosterone in an alcohol-free cream formulation (Wittert *et al.*, 2016) when administered to the scrotal skin.

MATERIALS AND METHODS

This was a single-center, three-phase cross-over pharmacokinetic study of three single doses in random sequence of testosterone cream [AndroForte 5, 5% w/v (50 mg/mL) testosterone cream; Lawley Pharmaceuticals, West Leederville, Australia] administered to healthy volunteers. To evaluate the pharmacokinetics of exogenous testosterone in eugonadal volunteers, endogenous testosterone production was suppressed throughout the study by injection of nandrolone decanoate. Healthy male volunteers aged 18–50 years were recruited by advertising and reimbursed for their time and travel costs to participate in the study. The inclusion criteria included no history of reproductive endocrine disorders or testicular pathology, normal kidney and liver function, and willingness to provide written informed consent and comply with all study requirements. The exclusion criteria were plans for paternity within the following year or working in an occupation (including elite athletes) that require urine drug screening, chronic medical illness requiring regular prescribed medication, contraindication to testosterone including prostate or breast cancer, untreated sleep apnea or polycythemia (hematocrit >0.52), history of androgen, or other drug abuse, HIV positivity or viral hepatitis, scrotal skin disease that may interfere with transdermal drug delivery, major psychiatric disease or psychological condition that may limit compliance with study requirements, regular medications that may interfere with dermal absorption or metabolism of testosterone or other conditions that may adversely affect study outcome or participant safety. The study was approved by the Sydney Local Health District Human Ethics Committee (Concord Hospital) within NHMRC/Australian Health Ethics Committee guidelines for human experimentation consistent with the Declaration of Helsinki. The study was registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12615000045516).

The primary endpoint was serum testosterone concentrations over 16 h measured by liquid chromatography, tandem mass spectrometry (LC-MS). The secondary endpoints were serum dihydrotestosterone (DHT) and estradiol (LC-MS) as well as tolerability. After two screening visits, participants attended five study visits over 11 days. They were administered two intramuscular injections of nandrolone decanoate (50 mg in 1 mL arachis oil vehicle) comprising 200 mg three days prior to and 100 mg four days after the first testosterone dose to suppress endogenous testosterone secretion throughout the study. The nandrolone dosage was selected as known to transiently suppress endogenous testosterone for the study period without adverse effects (Minto *et al.*, 1997; Handelsman *et al.*, 2009, 2014; Singh *et al.*, 2014). Each eligible, consenting participant was administered three single doses of testosterone cream in random sequence on different study days with at least 2 days wash-out period between studies. The testosterone doses were 50 mg (1 mL cream), 25 mg (0.5 mL cream) and 12.5 mg (0.25 mL cream) each drawn from the same tube for each participant with the volume (dose) of testosterone cream measured using 1 mL insulin syringe and verified by a separate investigator. A venous cannula was inserted to obtain three pre-dose baseline blood samples at 15, 5 min and immediately prior to application of the testosterone cream which was applied at 08:00 to the scrotum by the participant using a gloved hand. Blood sampling was then further undertaken at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, and 16 h post-cream application. Serum was stored frozen (−20 °C) until assay in a single batch. In addition, venous and finger-prick blood samples were spotted onto filter paper at 0, 4, 8, 12, 16, and 24 h and stored at room temperature in sealed plastic bags. To convert ng/mL to ng/dL, multiply ng/mL by 100. To convert ng/mL to SI units (nM) multiply by 3.47 for testosterone and 3.45 for DHT and to convert pg/mL to SI units (pM) multiply by 3.68 for estradiol.

Assays

Serum testosterone, DHT, and estradiol were measured in solvent extracts (methyl tert- butyl ether) by liquid chromatography, tandem mass spectrometry as described in detail elsewhere (Harwood & Handelsman, 2009; Singh *et al.*, 2014) in the Andrology laboratory, ANZAC Research Institute. Dried blood spots were extracted for concurrent measurement of testosterone and nandrolone as described (Singh *et al.*, 2014). The limits of detection and coefficients of variation (range for three quality control samples run in triplicate in each run) were 10 pg/mL (35 pM) and 3–6% for testosterone, 50 pg/mL (173 pM) and 9–11% for DHT and 1 pg/mL (4 pM) and 7–13% for estradiol. For calculations involving undetectable serum DHT concentrations, the concentration was imputed as half the lowest detectable concentration. Reference ranges for circulating steroid concentrations were 1.8–7.8 ng/mL (6.2–26.9 nM) for testosterone, 0.07–0.64 ng/mL (0.24–2.21 nM) for DHT, and 15–68 pg/mL (55–250 pM) for estradiol based on 95% confidence intervals determined from a study of 382 healthy young men aged around 20 years old from a population-based birth cohort study (Hart *et al.*, 2015).

Data analysis

In order to take into account the cross-over design which features participants as their own controls for each dose, the time-

courses of serum testosterone, DHT or estradiol concentrations were analyzed for main (between) effects of dose and time, and their interaction, for a mixed model linear analysis for repeated (within-subject) measures employing restricted maximum likelihood minimization with a first-order autoregressive variance–covariance structure, which was optimal according to the lowest Akaike information criterion. Pharmacokinetic variables [peak concentration (Cmax), time of peak concentration (Tmax)] were estimated empirically from the serial concentrations of steroids as well as estimated from the fitted concentration-time curves formed by nonlinear curve fitting to a bi-exponential model of concentrations (C) as a function of time (T) since testosterone dose administration according to the functional form C = a*exp (-b*T)+c*exp(-d*T). From fitted models, Tmax is estimated as ln (-cd/ab)/(d-b), AUC as a/b+c/d and 95% confidence intervals for model-based estimates of Cmax and Tmax were derived from 3000 bootstrap estimates. All data analysis used NCSS 11 Statistical Software (NCSS, LLC. Kaysville, UT, USA, www.ncss.com) and calculations according to standard pharmacokinetic methods (Gibaldi & Perrier, 1982).

RESULTS

The details of participants are in Table 1. Eleven men completed 12 full cycles of three testosterone doses in random sequence. One man completed a second cycle after an interval of 3 months from his first participation. All participants had normal renal (serum urea, creatinine) and liver (serum albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase) function tests, and full blood counts (hemoglobin, leukocytes, platelets). [Correction added on April 28, 2017, after online publication: The number of participants in the study has been added to this paragraph.]

Pre-study administration of nandrolone effectively suppressed serum testosterone by 95% to castrate levels ($p < 0.0001$) and DHT by 80% ($p = 0.01$) but did not suppress serum estradiol ($p = 0.31$).

Table 1 Details of participants

Variable	Mean (SEM)	Median (Q1, Q3)	Range
Age (year)	34.3 (3.0)	34.5 (24.4, 43.6)	20–48
Height (cm)	177 (1)	176 (174, 178)	173–186
Weight (kg)	75.3 (2.5)	74.3 (67.1, 82.1)	61–88
BMI (kg/m^2)	24.0 (0.7)	24.1 (21.3, 26.3)	20.4–27.8
BSA (m^2)	1.93 (0.04)	1.93 (1.82, 2.01)	1.72–2.14
Mean testis volume (mL)	21 (1)	21 (19, 25)	15–28
Hemoglobin (g/L)	158 (3)	156 (154, 166)	141–173
Serum testosterone (ng/mL)			
Screening[a]	4.1 (0.3)	3.8 (2.4, 5.4)	1.9–7.3
Pre-study[b]	0.5 (0.1)	0.2 (0.2, 0.5)	0.1–3.1
Serum DHT (ng/mL)			
Screening[a]	0.14 (0.02)	0.14 (0.03, 0.22)	0.03–0.38
Pre-study[b]	0.1 (0.01)	0.03 (0.03, 0.1)	0.03–0.33
Serum estradiol (pg/mL)			
Screening[a]	16 (1)	16 (11, 19)	5–30
Pre-study[b]	18 (2)	11 (7, 26)	3–59

To convert ng/mL to ng/dL, multiply ng/mL by 100. To convert ng/mL to SI units (nM) multiply by 3.47 for testosterone and 3.45 for DHT and to convert pg/mL to SI units (pM) multiply by 3.68 for estradiol. [a]Mean of two screening serum samples per participant. [b]Mean of three pre-study samples at times 15, 5 and 0 min before administration of each of the three testosterone doses. All pre-study samples are after the first dose of nandrolone decanoate noting the marked suppression of serum testosterone.

Administration of testosterone to the scrotal skin produced a swift increase in serum testosterone with significant effects of dose ($p < 0.0001$), time ($p = 0.003$) and the time x dose interaction ($p = 0.04$) (Fig. 1). After administration of testosterone, serum DHT concentrations demonstrated significant effects of time ($p < 0.0001$) but neither the dose ($p = 0.35$) nor the time x dose interaction ($p = 0.08$) had statistically significant effects on serum DHT. For serum estradiol, there was no significant effects of testosterone administration on dose ($p = 0.057$), time ($p = 0.057$) or their interaction ($p = 0.60$) (Fig. 2).

After testosterone administration, the peak concentration of serum testosterone was dose dependent with the time of peak being between 1.9 to 2.8 h after doses (Table 2). Serum DHT rose to a peak concentration between 1.0 and 1.4 ng/mL (3.5–4.8 nM) between 4.1 and 5.6 h after testosterone administration, but the peak times and concentrations were not dose dependent. Using data from pooling the three testosterone doses, the estimated peak serum DHT concentration was 1.2 ng/mL (4.1 nM) and occurred at 4.9 h. When time of peak was determined empirically, there were similar trends to later time of peak concentration of serum DHT compared with serum testosterone (Table 2). Serum estradiol did not display any significant changes in time of peak or of peak concentrations with testosterone dose (Fig. 3).

All doses were well tolerated without complaint of skin irritation or discomfort.

DISCUSSION

This study provides a pharmacokinetic profile of three doses of testosterone administered to the scrotal skin in a cream formulation. Application of the testosterone cream produced a rapid rise in serum testosterone peaking around 2 h after administration with a dose-dependent peak concentration, but not any consistent relationship between time of peak and testosterone

Figure 1 Serum testosterone following three doses (12.5, 25, 50 mg) of testosterone cream applied to the scrotal skin at time zero with sequential blood sampling at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 and 16 h. Each participant underwent scheduled blood sampling after administration of each of the three doses with at least 2 days between administration and sampling periods. S1 and S2 are two screening blood samples taken prior to the study and P1 and P2 are two blood samples taken 15 and 5 min prior to the application of the testosterone cream. Data are plotted as mean and standard error of the mean. Biexponential curves are fitted to all the data for each dose. For further details see the text. Note conversion factors: to ng/dL multiple ng/mL by 100; to SI units multiply ng/mL by 3.47. [Colour figure can be viewed at wileyonlinelibrary.com].

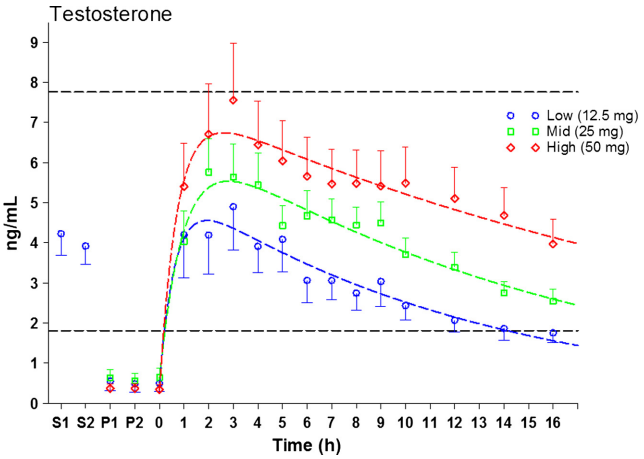


Figure 2 Serum dihydrotestosterone (DHT) following three doses (12.5, 25, 50 mg) of testosterone cream applied to the scrotal skin at time zero with sequential blood sampling at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, and 16 h. Each participant underwent scheduled blood sampling after administration of each of the three doses with at least 2 days between administration and sampling periods. S1 and S2 are two screening blood samples taken prior to the study and P1 and P2 are two blood samples taken 15 and 5 min prior to the application of the testosterone cream. Data are plotted as mean and standard error of the mean. A biexponential curve is fitted to all the data combined as the time course was not significantly different between doses. For further details see the text. Note conversion factors: to ng/dL multiple ng/mL by 100; to SI units multiply ng/mL by 3.45. [Colour figure can be viewed at wileyonlinelibrary.com].

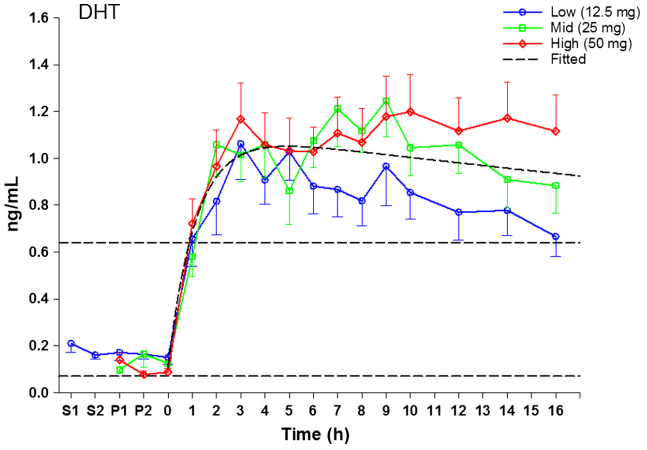
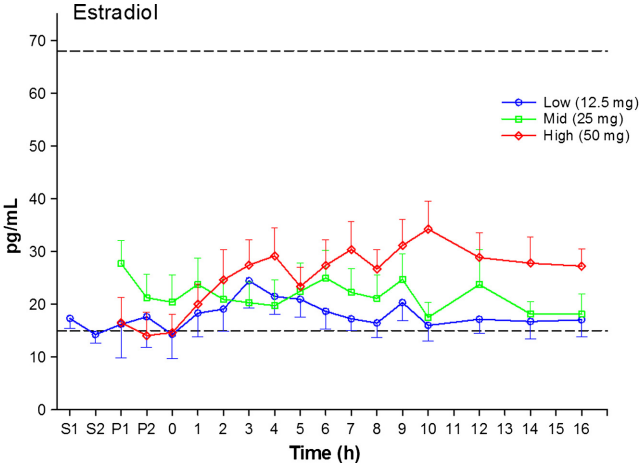


Figure 3 Serum estradiol following three doses (12.5, 25, 50 mg) of testosterone cream applied to the scrotal skin at time zero with sequential blood sampling at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 and 16 h. Each participant underwent scheduled blood sampling after administration of each of the three doses with at least 2 days between administration and sampling periods. S1 and S2 are two screening blood samples taken prior to the study and P1 and P2 are two blood samples taken 15 and 5 min prior to the application of the testosterone cream. Data is plotted as mean and standard error of the mean. No curve was fitted as there was no significant effect of dose, time or their interaction on serum estradiol. For further details see the text. Note conversion factors: to pg/dL multiple pg/mL by 100; to SI units multiply pg/mL by 3.68 sec. [Colour figure can be viewed at wileyonlinelibrary.com].



dose. At the lowest dose (12.5 mg), the serum testosterone concentrations were maintained in physiological range for at least 12 h and with the 25 mg dose maintained serum testosterone concentrations within the physiological range for nearly 24 h concentration.

Dose–response pharmacokinetics of testosterone delivered via the scrotal skin route has been examined in one previous study. In the original transdermal testosterone studies using a scrotal patch, six men with primary hypogonadism were administered patches containing 0, 5, 10 or 15 mg of testosterone daily for a week. These scrotal transdermal patches produced a dose-dependent and reproducible increase serum testosterone concentration at the end of study which were maintained within the physiological range throughout 24 h (Findlay *et al.*, 1987). However, the effects of single doses were not examined, the amount of testosterone actually delivered to the scrotal skin was not defined nor was serum DHT measured. Furthermore, the non-suppressed endogenous testosterone made it impossible to distinguish it from exogenous testosterone which clouded interpretation of apparent between-individual variations in dermal absorption (Findlay *et al.*, 1989). Subsequently, virtually all studies employed only a single testosterone transdermal patch with the limited scrotal skin area available posing an inherent limitation on dose–response studies.

The bioavailability of testosterone via the scrotal skin is striking higher than for abdominal skin. Using the same testosterone cream and steroid LC-MS assay measurements, in this study a Cmax (4.6 ng/mL, 16.0 nM) was achieved with the lowest dose (12.5 mg) applied to the scrotal skin whereas applying 100 mg testosterone cream to the abdominal skin produced a Cmax of 16.3 nmol/L (4.7 ng/mL). This suggests an about eightfold

Table 2 Pharmacokinetic parameters of serum testosterone and DHT after administration of testosterone to scrotal skin by testosterone dose in a three-way cross-over study

Dose	Testosterone			DHT		
	Low (12.5 mg)	Mid (25 mg)	High (50 mg)	Low (12.5 mg)	Mid (25 mg)	High (50 mg)
Empirical[a]						
Tmax (h)	3.3 (0.6)	5.3 (0.9)	4.9 (0.7)	6.6 (0.8)	7.2 (0.8)	8.8 (1.1)
Cmax (ng/mL)	5.7 (1.1)	6.3 (0.8)	8.3 (1.3)	1.3 (0.1)	1.4 (0.2)	1.4 (0.2)
Model estimated						
Tmax[b] (h)	1.9	2.8	2.6	4.1	5.6	4.9
Cmax[c] (ng/mL)	4.6 (3.5, 5.5)	5.5 (4.8. 6.2)	6.8 (5.7, 7.7)	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
$C_{24\ h}$ (ng/mL)	0.8	1.6	3.0	0.5	0.8	1.2
AUC_{∞} (ng/mL*h)	112	129	229	79	104	NE[d]

Note conversion factors: to ng/dL multiple ng/mL by 100; to SI units multiply ng/mL by 3.47 for testosterone and 3.45 for DHT. [a]Mean and standard error of the mean from serial concentrations. [b]Time of peak concentration as a function of parameters from bi-exponential curve fit. [c]Mean and 95% confidence intervals for peak concentration from bootstrap estimation. [d]NE not estimable due to non-convergent curve.

increase in testosterone bioavailability, using the scrotal compared with abdominal skin routes. This has useful practical implications given the wide between-person variability in dermal bioavailability with application to truncal skin. For example, in studies of a testosterone gel that permitted up and down titration of dose aiming for optimal circulating testosterone concentrations, men who required up-titration (ie had lower skin bioavailability) still had lower steady-state circulating testosterone than men who were either up-titrated (higher dermal bioavailability) or not titrated during the study (Wang *et al.*, 2004). Hence this study supports the concept that application of testosterone to the scrotal skin may overcome the lower dermal bioavailability of some individuals.

One previous study has reported that the pharmacokinetics of scrotal application of testosterone gel was similar to that of a scrotal testosterone patch or a fivefold larger dose of non-scrotal testosterone gel, consistent with at least a fivefold higher transdermal bioavailability of testosterone (Kuhnert *et al.*, 2005). Other studies assessing pharmacokinetics of testosterone application to non-scrotal skin have yielded variable time of peak concentration (Tmax) ranging from 6–16 h (Marbury *et al.*, 2003; Miller *et al.*, 2011; Olsson *et al.*, 2014) but similar peak concentration (Cmax) as scrotal skin application (Rolf *et al.*, 2002; Bouloux, 2005; Olsson *et al.*, 2014). Although most studies revealed a marked delay in peak serum testosterone concentration, another study of 100 mg testosterone gel applied to non-scrotal skin in hypogonadal men reported rapid absorption kinetics and higher Cmax (≥13.4 ng/mL) (Wang *et al.*, 2000). However, in that study, the residual endogenous testosterone in these men left it unclear in that study how much was attributable to the exogenous testosterone.

Testosterone administration to the scrotal skin also produced a marked rise in serum DHT following each testosterone dose, but neither the time of peak nor the peak DHT concentration were dose dependent. The peak serum DHT concentrations (1.0–1.4 ng/mL; 3.5–4.8 nM) were higher than prevailing among healthy eugonadal men and characteristically peaked between 4–6 h after a testosterone dose, thereby between 2–3 h later than serum testosterone peaked. This time delay is most consistent with the conversion of testosterone to DHT occurring within a skin (stratum corneum) depot with delayed release, whereas if the 5-α reductase conversion occurred in the circulation, it is likely there would have been little or no delay relative to serum testosterone concentrations. Disproportionate increases in serum DHT after scrotal administration of testosterone have long been noted (Bals-Pratsch *et al.*, 1986; Ahmed *et al.*, 1988) although previous studies measured DHT, using immunoassays, some unspecified (Korenman *et al.*, 1987), which are less accurate and specific than the LC-MS measurements used in this study.

Disproportionate increases in serum DHT are reported after administration of all transdermal testosterone products with the higher DHT/T ratio attributable to the strong expression of 5-alpha reductase in skin structures which foster the conversion of testosterone to DHT during transdermal passage. Furthermore androgens induce greater expression of the 5α reductase enzyme whereby administration of an androgen directly onto the skin creates a feed-forward (positive feedback) mechanism (Russell & Wilson, 1994; McNamara *et al.*, 2013). Analogous disproportionate increases in serum DHT (creating a higher DHT/T ratio) are also reported after oral testosterone undecanoate (Schnabel *et al.*, 2007; Yin *et al.*, 2012). The clinical significance of such increased DHT/T ratio, common to all non-parenteral routes of testosterone administration, is doubtful as studies maintained circulating DHT levels of 10 times the physiological concentrations for up to 2 years without increasing prostate size or growth or any adverse sequelae (Idan *et al.*, 2010) nor do exogenous androgens increase intraprostatic DHT (Marks *et al.*, 2006; Page *et al.*, 2011; Mostaghel *et al.*, 2012; Thirumalai *et al.*, 2016).

The strengths of this study include the detailed blood sampling after single applications of a range of testosterone doses (12.5, 25, 50 mg) to better define the pharmacokinetics of the scrotal skin route, the use of nandrolone to suppress endogenous testosterone to allow an investigation of testosterone pharmacokinetics without interference by endogenous testosterone, and the use of LC-MS measurement of all steroids.

The limitations of this study are that it investigated only a single administration so that long-term steady-state findings could not be studied. The use of nandrolone to suppress endogenous testosterone could, in theory, modify skin or other organs which might influence testosterone absorption or metabolism and, while it cannot be excluded, this possibility would not interfere with interpretation of our findings relevant to the different testosterone doses studied in random sequence under the same conditions.

We conclude that the scrotal administration of testosterone in a cream formulation provides high bioavailability, dose-dependent peak serum testosterone concentration, and tolerability with a much lower dose relative to the non-scrotal transdermal route. Further studies of extended duration will be required to fully evaluate the clinical application of this new scrotal testosterone formulation.

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