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Transdermal Testosterone

Karen J. McClellan and *Karen L. Goa*

Adis International Limited, Auckland, New Zealand

Contents

Summary

▲ Nightly application of testosterone transdermal (TTD) system to nonscrotal sites in men with hypogonadism results in a 24-hour serum testosterone concentration profile which mimics the circadian pattern observed in healthy young men.

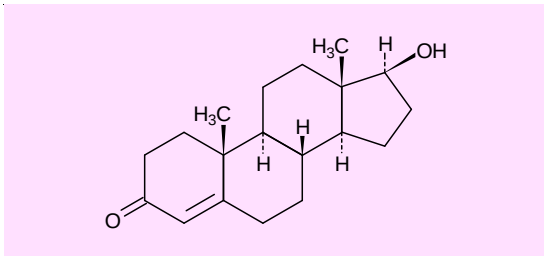
▲ The system also normalises dihydrotestosterone/testosterone and estradiol/testosterone ratios and reduces luteinising hormone levels towards the normal range.

▲ A multicentre, open-label study demonstrated that nocturnal erectile response and overall sexual function improved during 12 months' treatment with the TTD system (5 mg/day) in men with hypogonadism. Individual variables of sexual desire, arousal, frequency of sexual activity, orgasm and satisfaction also improved.

▲ The TTD system is well tolerated, with application site reactions such as pruritus, burn-like blisters and erythema being the most commonly reported events.

▲ Prostate-specific antigen levels and prostate volume remain in the normal range during long term treatment.

Features and properties of transdermal testosterone	
Indications	
Hypogonadism	Launched
Mechanism of action	
Androgen	Male gonadal hormone
Dosage and administration	
Usual dosage in clinical trials	5 mg/day
Route of administration	Transdermal
Site of application	Nonscrotal skin
Frequency of administration	Once daily at night
Pharmacokinetic profile (2 patches releasing a total of 5 mg/day)	
Peak serum concentration	25.6 nmol/L
Time to peak serum concentration	8.54h
Area under the serum concentration-time curve	108 μg/L • h
Clearance	54.3 L/h
Elimination half-life	1.29h
Adverse events	
Most frequent	Application site reactions including pruritus, burn-like blisters and erythema



Testosterone

Male hypogonadism is a disorder whereby testosterone production is reduced below the normal range of 3 to 10 mg/day.[1] It results in diminished sexual and reproductive function as well as impaired muscle and carbohydrate metabolism, bone mineralisation, immune function and mood.[1]

Currently available androgen replacement modalities include intramuscular injection of long-acting testosterone esters and oral administration of alkylated and esterified testosterone. However, neither of these treatments delivers testosterone in a manner which produces plasma levels mimicking normal circadian profiles of the endogenous hormone.[1]

More recently, a testosterone transdermal (TTD) system has been developed for use as an androgen replacement therapy for hypogonadal males. The system uses a permeation-enhancing formulation composed of testosterone (12.2 and 24.3mg in the 2.5 and 5mg systems, respectively), water, ethanol, pharmaceutical lipids and gelling agents.[2] In contrast to another available transdermal system, it is designed for application to non-scrotal rather than shaved scrotal sites.[3]

1. Pharmacodynamic Profile

- Daily application of two 2.5mg TTD systems at approximately 2200h for 12 months in 34 hypogonadal men resulted in a 24-hour serum testosterone concentration profile which mimicked the normal circadian pattern observed in healthy young men, with a morning peak (25.7 nmol/L) and a night-time trough (7.4 nmol/L).[4] Mean testosterone levels, measured 12 hours after application of two 2.5mg TTD systems, were normalised (range 18.1 to 22.3 nmol/L) in 93% of patients.[4,5] Levels of testosterone (mean 20.8 nmol/L), bioavailable testosterone (mean 11.1 nmol/L), dihydrotestosterone (mean 1.6 nmol/L) and estradiol (mean 99 pmol/L) were within the normal physiological range during months 3 to 12 of treatment.[5]

- In 6 men with hypogonadism who received TTD systems for 28 days, the ratios of plasma dihydrotestosterone/testosterone and estradiol/testosterone were within the normal range (0.07 and 0.005, respectively).[6] Plasma levels of sex hormone-binding globulin were not significantly altered.[6]

- Continuous TTD treatment caused suppression of the pituitary/gonadal axis in men with hypogonadism, resulting in a reduction in serum luteinising hormone (LH) levels towards normal.[5] In 5 of 9 patients with primary hypogonadism, LH levels were normalised after 3 to 6 months' treatment.[5]

2. Pharmacokinetic Profile

Absorption

- The back, thigh, upper arm and abdomen were identified as the optimal sites of TTD application in a group of 34 hypogonadal men. A single application of two 2.5mg TTD systems to these sites resulted in average testosterone absorption of 4 to 5mg over 24 hours,[7] which is within the normal physiological range of endogenous testosterone production (3 to 10 mg/day).[6] Testosterone was absorbed at a faster rate during the first 12 hours than during the last 12 hours.[7] Applications to the chest and shins produced greater interindividual variation and lower average absorption of testosterone over 24 hours (3 to 4mg)[7] and thus are not recommended sites.

- After night-time application of 1, 2 or 3 TTD systems (releasing approximately 2.5, 5 or 7.5 mg/day testosterone) to the middle back regions of 12 men with hypogonadism, area under the serum concentration-time curve (AUC) values and peak serum testosterone concentrations (C_{max}) increased in a dose-related manner.[8] After application of two

2.5mg systems, mean C_{max} levels (25.6 nmol/L) were reached within 6 to 12 hours (t_{max}: mean 8.54 hours). C_{max} levels were within the normal range for the 1- and 2-system dose regimens, but were above or near the upper limit of normal after the 3-system application (however, this is not the usual recommended dose). Mean testosterone AUC after a 5 mg/day TTD regimen was 108 μg/L · h.[8]

• In 20 men with hypogonadism, a single 5mg TTD system produced a serum testosterone concentration profile which was similar to that produced by two 2.5mg systems, indicating bioequivalence. C_{max} values were 31.4 and 32.1 nmol/L, respectively.[9]

Metabolism and Elimination

• Circulating testosterone, whether from endogenous or exogenous sources, is metabolised to dihydrotestosterone by 5 α-reductase and to estradiol by an aromatase enzyme complex found in the liver, fat and testes.[3]

• Testosterone released from the TTD system has an apparent elimination half-life ($t_{½}$) of 1.29 hours[7] and a systemic clearance of 54.3 L/h.[10] Serum testosterone concentrations return to hypogonadal levels within 24 hours after system removal.[10]

• Data on excretion of a TTD dose are lacking. However, 90% of an intramuscular testosterone dose is excreted as glucuronide and sulphate conjugates in the urine; about 6% is excreted in the faeces.[10]

• Triamcinolone 0.1% cream had no significant effects on the pharmacokinetics (e.g. C_{max}, t_{max}) of the TTD system when applied as a pretreatment to the site of patch administration in 16 men with hypogonadism.[11]

3. Therapeutic Trials

The clinical effects of the TTD system have been investigated in several open-label trials in men with hypogonadism. However, the results of only 1 of these studies have been published in full to date. This study (the results of which have been presented in 4 separate reports)[4,5,7,12] evaluated the influence of application site on the pharmacokinetics of the TTD system[7] (section 2), as well as the effects of the TTD system on sexual function[4] (see below), prostate size[12] (section 4) and hormone levels[4,5] (section 1).

The study which was multicentre included 34 men aged 21 to 65 years with primary or secondary hypogonadism (morning serum testosterone levels ≤8.7 nmol/L). All men had received prior androgen replacement therapy (generally intramuscular testosterone) for ≥3 months. After an 8-week androgen washout period, patients applied 2 TTD systems (each delivering approximately 2.5mg testosterone per day) every evening to the back, abdomen, upper arms or thighs on a rotating basis for 12 months. 29 patients (9 with primary and 20 with secondary hypogonadism) completed the study and were included in the overall evaluation; 20 were eligible for the evaluation of erectile response. The effects of the TTD system on sexual function are reported below.

• Nocturnal erectile response improved during treatment with the TTD system. Significant increases were reported in the number of erectile events per hour ($p = 0.047$), the mean duration of events ($p = 0.014$), mean rigidity ($p = 0.001$) and the erectile index for the base and tip of the penis ($p = 0.002$) compared with the androgen withdrawal period.[4] Responses were similar to those reported during previous treatment with intramuscular testosterone.[4]

• Overall sexual function as assessed by the total Watts questionnaire score increased significantly ($p = 0.003$) during treatment with the TTD system compared with the androgen withdrawal period.[4] Individual variables of sexual desire, arousal, frequency of sexual activity, orgasm and satisfaction showed similar patterns (fig. 1).[4] The effects of transdermal testosterone were sustained for the entire 12-month treatment period and were similar to those observed with intramuscular testosterone.[4]

• The mean number of erections per week, derived from the Davidson questionnaire results, was significantly greater during treatment with intra-

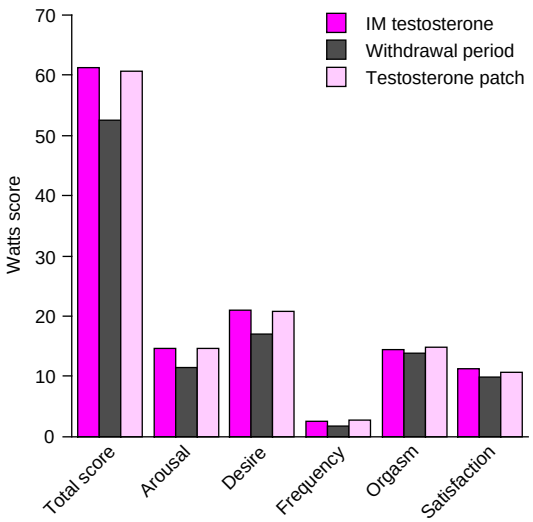


Fig. 1. Subjective assessment of the effects of transdermal testosterone on sexual function using the Watts questionnaire. Patients (n = 29) were assessed during intramuscular (IM) testosterone treatment followed by androgen withdrawal followed by transdermal testosterone treatment (5 mg/day). A higher score indicates a better result. All events in both treatment groups improved significantly compared with the withdrawal period ($p < 0.05$) except for satisfaction with overall sexual function in the transdermal testosterone group.[4]

muscular testosterone or the TTD system compared with the androgen withdrawal period (7.5 and 7.8 *vs* 2.3; $p < 0.001$).[4]

4. Tolerability

• Tolerability evaluations conducted in men with hypogonadism treated with TTD systems for up to 48 months showed that local reaction at the application site was the most commonly reported adverse event, occurring in 65 of 122 (53%) patients. Application site reactions included pruritus (37%), burn-like blisters (12%), erythema (7%) and vesicles (6%) [fig. 2] and resulted in treatment withdrawal in 9.8% of patients.[10,13]

• Other reactions included prostate abnormalities (5%), headache (4%), contact dermatitis (4%), burning at the application site (3%), induration at the application site (3%), depression (3%), rash (2%) and gastrointestinal bleeding (2%) [fig. 2].[10]

• 19 of 34 patients (56%) reported local skin irritation during a 1-year treatment period (reactions necessitated withdrawal in 3 patients).[4] The most commonly reported events included pruritus with mild to moderate erythema (15 patients) and itching (15 patients) at the application site. Six patients reported blisters, generally when the system had been applied over bony prominences.[4]

• Pretreatment of the application site with triamcinolone 0.1% cream significantly improved local tolerability (as assessed by erythema scores) in 16 men with hypogonadism who applied two 2.5mg TTD systems each night during the treatment period[11] and in 62 healthy male volunteers who applied one 2.5mg system each night for 6 weeks.[14]

Effects on the Prostate

• Mean prostate weight increased to approximately 18g in 29 hypogonadal men during 12 months' treatment with the TTD system.[12] This was similar to that reported during 12 months' previous treatment with intramuscular testosterone (17g), but significantly greater than that reported during an intervening 8-week androgen with-

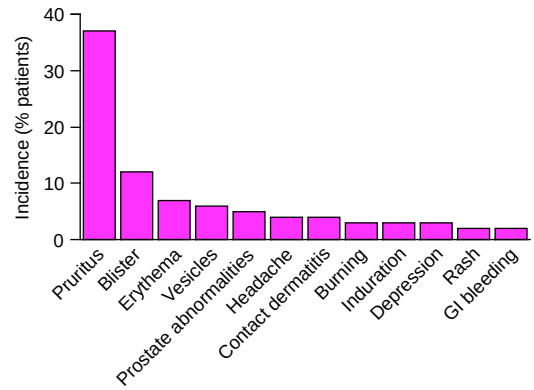


Fig. 2. Tolerability profile of transdermal testosterone. Most commonly reported adverse events in 122 men with hypogonadism who received transdermal testosterone systems for up to 48 months.[10,13]

drawal period (14g; $p < 0.001$).[12] No patient developed symptomatic benign prostatic hyperplasia during treatment.[12] Prostate volume during androgen replacement therapy approached that reported previously for healthy males.[15]

- In 16 previously untreated hypogonadal males who received a TTD system for 6 to 12 months, prostate volume increased compared with baseline but remained within the normal range (17.8 to 20.1ml).[16]

- Long term treatment (for 1 year) was not associated with abnormal serum prostate-specific antigen levels or an increased incidence of anatomical prostate abnormalities in 34 men with hypogonadism.[4] However, in 122 men treated with TTD systems for up to 48 months, 5% developed prostatic abnormalities.[10]

Effects on Plasma Lipids

- 12 months' treatment with the TTD system (5 mg/day) reduced plasma high density lipoprotein (HDL)-cholesterol levels by 7.6% ($p < 0.05$) and increased the total cholesterol/HDL-cholesterol ratio by 9% ($p < 0.05$) from baseline in 29 patients with hypogonadism.[5] However, the effects of the TTD system on plasma lipid levels were not significantly different from those reported during prior treatment with intramuscular testosterone.[5]

Effects on Haematocrit

- Men with hypogonadism who were treated for 24 weeks with the TTD system (5 mg/day) had fewer abnormal haematocrit elevations than those treated with intramuscular testosterone 200mg every 2 weeks.[17] Two of 26 men (8%) versus 8 of 32 men (25%) in the respective groups had elevated haematocrit levels at week 24 ($p < 0.05$). Values ranged from 39.6 to 53.6 with the TTD system and from 42.0 to 61.6 with intramuscular testosterone at study end.[17]

5. Transdermal Testosterone: Current Status

The permeation-enhanced TTD system, when applied to nonscrotal sites in men with hypogonadism, produces circulating testosterone levels which mimic the natural daily testosterone cycle. This improves clinical manifestations of androgen deficiency such as sexual dysfunction. Furthermore, except for local skin irritation, the preparation is well tolerated.

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Correspondence: *Karen J. McClellan*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz