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TOPIC PAPER

Louis J. G. Gooren · Mathijs C. M. Bunck

Transdermal testosterone delivery: testosterone patch and gel

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Abstract Testosterone replacement treatment is usually life-long. Fortunately, testosterone administration is relatively safe and until the age of 50 years few side effects are noted with normal doses of testosterone. After the age of 50 years when prostate disease becomes more prevalent, shorter-acting testosterone preparations, allowing a fast reduction of circulating testosterone levels, may be an advantage. Testosterone has an impact on sexual and non-sexual behaviour and short-acting testosterone preparations may be better suited for the initiation of long-term administration allowing the monitoring of behavioural effects. Testosterone can be delivered to the circulation through the intact skin, both genital and non-genital. Transdermal administration delivers testosterone at a controlled rate into the systemic circulation, avoiding hepatic first pass and reproducing the diurnal rhythm of testosterone secretion and without the peak and trough levels observed with the use of the traditional long-acting testosterone injections. In conclusion, both the testosterone patch and testosterone gel are valuable contributions to androgen replacement treatment meeting the requirements specified for testosterone replacement treatment.

Keywords Androgen replacement therapy · Testosterone patch · Testosterone gel · Hypogonadism

Hypogonadism occurs in all age ranges. Serious complications of androgen treatment are rare and are typically age-related. Over the age of 50 years prostate disease, an androgen-related condition, becomes more common. While long-acting testosterone preparations offer great advantages in terms of convenience and compliance for younger patients, in elderly patients it is desirable that testosterone administration can be discontinued within a short period of time. Furthermore, the idiosyncratic behavioural reactions to testosterone administration are not predictable, and therefore, it may be advisable to start testosterone administration with a short-acting preparation. When no adverse behavioural effects occur, the patient can be shifted to a long-acting preparation. Transdermal testosterone preparations are well suited for the above purposes since plasma testosterone levels decline to pretreatment values over 24–72 h.

Testosterone can be delivered to the circulation through the intact skin, both genital and non-genital [4]. Transdermal administration delivers testosterone at a controlled rate into the systemic circulation, avoiding hepatic first pass and reproducing the diurnal rhythm of testosterone secretion and without the peak and trough levels observed in long-acting testosterone injections.

L. J. G. Gooren (✉) · M. C. M. Bunck
Section of Andrology of the Department of Endocrinology, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands
E-mail: ljg.gooren@vumc.nl
Fax: +31-20-4440502

Scrotal testosterone patch

The initial patches were first designed to deliver testosterone through the scrotal skin, where the permeability is five times greater than for other skin sites. It required weekly scrotal shaving and was difficult for some patients to apply and maintain in position for 24 h (for review see Atkinson et al. [2]).

The transdermal scrotal patch (60 mm in diameter, Testoderm, Alza) is a thin film containing 10–15 mg of unmodified testosterone and delivers 4–6 mg testosterone per day to the circulation. Patients using the transscrotal testosterone delivery experience significant improvements in sexual function, sense of well being, mood and energy. The patch is worn for 22–24 h, and

the scrotum must be hair free for proper adhesion. After application plasma testosterone levels rise to a maximum 2–4 h later and remain within the midnormal range for the next 22–24 h. After removal plasma testosterone levels fall very rapidly. A study in 11 hypogonadal men for 7–10 years showed that plasma testosterone levels remained within the normal range for the full treatment period [3].

Prostate volumes slightly increased but did not exceed the size in a comparison group. Likewise, prostate specific antigen (PSA) levels increased but remained within the normal range. The pharmacokinetic profile met specifications as formulated in the World Health Organisation's (WHO) requirements of testosterone substitution. Transdermal scrotal testosterone administration is associated with high levels of 5α-dihydrotestosterone (DHT) as a result of high concentrations of 5α-reductase in the scrotal skin [2]. While non-physiological, the elevation of plasma DHT has probably little pathophysiological significance. Long-term use of DHT as androgen replacement treatment has no significant side effects [5, 13]. The patch may be irritating, and the use is not feasible if the scrotal surface is not adequate, which is sometimes the case in hypogonadal men. To overcome these limitations, non-scrotal skin patches have been developed (Fig. 1).

Non-scrotal testosterone patch

These patches (Androderm, Watsons) have a reservoir containing testosterone with a permeation-enhancing vehicle and gelling agents [10]. Patches that deliver natural testosterone in the amounts of 5 mg/day [2.5 mg for teenagers and 7.5 mg for men with a body mass index (BMI) far above average] are applied at night on rotating sites on the back, abdomen, upper arms and thighs. The cumulative transfer from the patch to the circulation was 5.48 ± 2.48 mg with 60% delivered during the first 12 h. The delivery system produces serum testosterone levels with a normal diurnal variation and normal plasma levels of DHT and 17β-oestradiol (E_2) [9]. Improvements have been reported in sexual function, libido, energy level and mood [1, 10].

The most common adverse effects are local skin reactions. Fifty percent of men participating in a clinical trial reported transient, mild to moderate erythema at some time during therapy [9]. Generalised allergic dermatitis requiring discontinuation of therapy occurred occasionally. Burn-like blister reactions occurred in 12% of the men [7].

However, most of these reactions were associated with application of the patch over a bony prominence or on parts of the body that could have been subject to

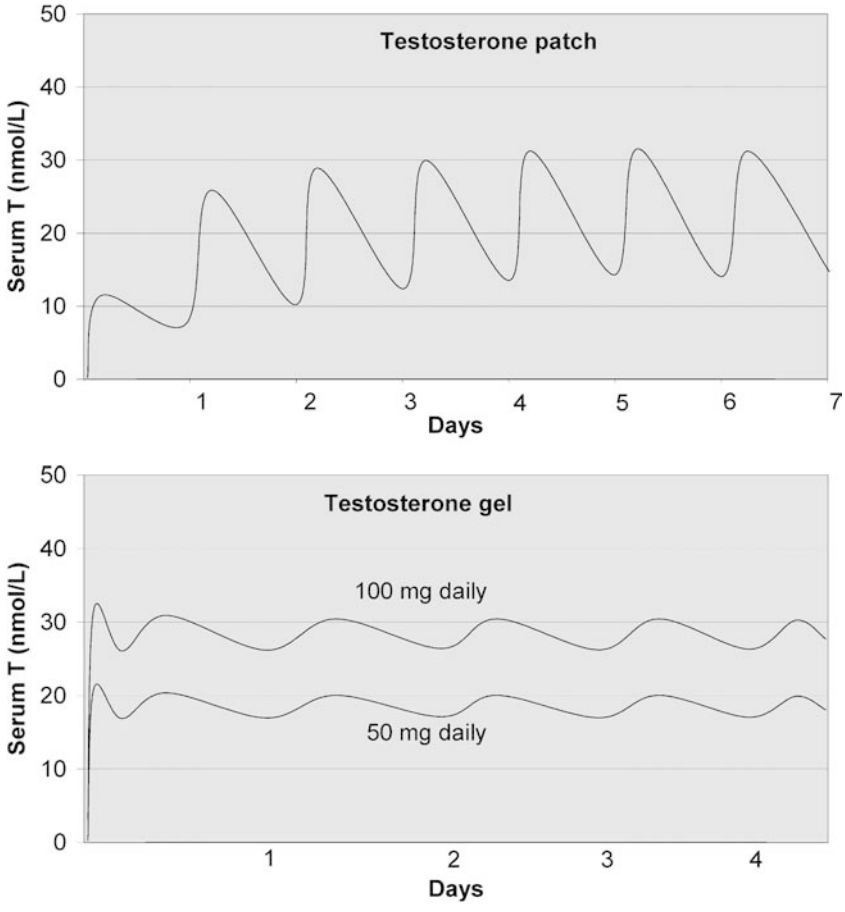

Fig. 1 Serum testosterone concentrations in different transdermal forms of application

prolonged pressure during sleep or sitting. Pre-treatment of the application site with triamcinolone acetonide cream decreases the skin reactions [19]. Clinical efficacy was as good as with conventional testosterone ester injections.

With regard to drug safety of the testosterone transdermal system, values of PSA and prostate volume [assessed by transrectal ultra sound (TRUS)] increased. As can be expected, when plasma testosterone levels are normalised prostate functions become normal, but both prostate size and PSA values remained within normal ranges. No clinically significant changes in lipids or results of serum chemistry studies were observed [1, 9].

Testosterone gel

Testosterone gel has been introduced for replacement therapy. Testosterone gel is hydro-alcoholic, 1% (10 mg testosterone per gram gel) and administered in a dose of between 5 and 10 g of gel per day, amounting to 50 and 100 mg testosterone per day. The pharmacokinetics of testosterone gel have been extensively studied. Serum testosterone levels rose 2–3 fold 2 h after application and rose further to 4–5-fold after 24 h. Thereafter, serum testosterone remained steadily in the upper range of normal and returned to baseline within 4 days after termination of application of testosterone gel. Mean DHT levels followed the same pattern as testosterone and were at or slightly above the normal adult male range. Serum E_2 levels rose and followed the same patterns as testosterone. The application of the testosterone gel at one site or four sites did not have a substantial impact on the pharmacokinetic profile [16].

Later studies showed that 9–14% of the testosterone administered is bioavailable. Steady state testosterone levels are achieved 48–72 h after the first application. Serum testosterone and free testosterone are similar on days 30, 90 and 180 after start of the administration, so there is no increase in metabolism over time. Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were suppressed proportionally to the levels of serum testosterone. Only with 100 mg testosterone gel was a suppression of sex hormone binding globulin (SHBG) noted, but not with the 50-mg dose. The formulation of the testosterone gel allows easy dose adjustments (50–75–100 mg testosterone gel) [15].

The clinical efficacy of transdermal testosterone gel on various androgen-dependent target organ systems has been very well documented. The safety profile showed that PSA levels rose in proportion to the increase of testosterone levels, but did not exceed normal values. Skin irritation was noted in 5.5% of patients in the study [17, 18]. Later studies with a 2.5% testosterone gel showed that 5 g of this gel achieved physiological serum testosterone levels in men whose endogenous testosterone production was pharmacologically suppressed with luteinizing hormone-releasing hormone (LHRH) agonists. These levels were reached after approximately 10 days. Serum DHT and E_2 did not exceed normal levels. Remarkably, washing of the site of application 10 min after application of the gel did not affect pharmacokinetic profiles [12]. The same authors could establish that washing of the site of application reduced the amount of testosterone that could be recovered from the site of application. Transfer from one person to another was found to be insignificant. No increase of serum testosterone was found after intense rubbing of skins with persons whose endogenous testosterone levels had been suppressed [12].

The commercially available testosterone gel is AndroGel (manufactured by Besins-Iscovesco, Paris; supplied in the U.S.A. by Unimed Pharmaceuticals, Inc., Buffalo Grove, Ill.). Recently, a new testosterone gel preparation has been developed: Testim (Auxilium Pharmaceuticals Inc, Norristown, Pa.). Its clinical efficacy was recently demonstrated [14]. Similar to Androgel, Testim is a 1% testosterone gel. One study claims that in 29 hypogonadal subjects receiving 50 mg testosterone of the new testosterone gel (Testim), the maximal concentrations of testosterone, DHT and free testosterone were respectively 30, 19 and 38% greater than with a similar dose of Androgel. Similarly, the areas under the curves (0–24 for total testosterone, DHT and free testosterone were respectively 30, 11 and 47% larger with Testim than with Androgel [6]. In a clinical study the mean increase after 90 days of Testim administration were 12.41 nmol/l testosterone with the 100 mg testosterone gel and 6.54 nmol/l for the 50 mg testosterone gel. A positive effect was noted on mood and libido and erections. Lean body mass increased and fat mass decreased with both dosages [8]. There is presently no obvious explanation why the pharmacokinetics of Testim would be superior to those of Androgel, and further comparison studies are required to substantiate superiority of one over the other.

Conclusions

The conclusion is warranted that transdermal delivery of testosterone to the circulation largely meets the requirements specified for testosterone replacement treatment [11]. Both the testosterone patch and the testosterone gel deliver amounts of testosterone that generate physiological levels of plasma testosterone between two administrations. For some of its actions, testosterone is a prohormone that is converted locally in tissue to DHT and 17β-oestradiol. With transdermal delivery of testosterone, plasma levels of these two conversion products lie largely in the physiological range except for the scrotal patch, which generates higher than normal plasma DHT, with probably no significant pathophysiological significance. These forms of treatment mimic the circadian rhythm of plasma testosterone; it is not clear, however, whether it has physiological significance.

As far as the preparations have been studied, no adverse effects on the prostate, serum lipids, liver or

respiratory function have been noted. Similar to oral preparations, transdermal testosterone preparations are patient-friendly, with a relative independence from medical services. The rapid reduction of circulating plasma testosterone after termination of administration is an asset when complications of testosterone occur. When testosterone administration is initiated with a short-acting preparation, potentially adverse behavioural effects of testosterone are more amenable to correction.

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