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Short review (expert opinion)

Transdermal delivery of testosterone

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ABSTRACT

Male hypogonadism has been treated with exogenous testosterone since the 1930s. The early transdermal patches of testosterone became available in the 1980s with gel and solution preparations following subsequent decades. This review focusses on the skin permeation characteristics of testosterone, pharmacokinetics following application of transdermal formulations and formulations currently available. At present, gels dominate the market for transdermal testosterone replacement therapy, presumably because of their greater patient acceptability and non-occlusive nature compared with patches. However, specific incidences of secondary transfer of gels to children with consequent unwanted effects such as precocious puberty have been reported. A regulatory review of all testosterone replacement therapies is currently underway which may have implications for future prescribing practices of transdermal testosterone products.

1. Introduction

Testosterone (Fig. 1) is an androgenic steroid hormone which regulates a number of important functions in males including sperm production, sex drive, fat distribution, muscle mass, bone density and red blood cell production. Production of testosterone in the testes is regulated by luteinizing hormone (LH) in the pituitary gland. Puberty starts with the production of LH and follicle-stimulating hormone (FSH), the latter hormone being critical for spermatogenesis. The action of testosterone is via the androgen receptor, located in the nucleus and cytoplasm of target cells. Deficiency or absence of testosterone in men is defined as hypogonadism which is further classified as either primary (originating in the testes) or secondary (resulting from a problem in the hypothalamus or pituitary gland). Testosterone deficiency may result from autoimmune conditions (Addison's disease or hypoparathyroidism), genetic disorders (Klinefelter's or Turner's syndrome) or may result for other reasons including accidents, infection, excessive exposure to heavy metals or alcohol, radiation, chemotherapy and tumours. With age, males experience declining testosterone levels and loss of the normal diurnal rhythm of testosterone which may also result in clinical hypogonadism [1].

The symptoms of hypogonadism include impaired libido, loss of sexual function, regression of secondary sex characteristics, low muscle mass and decreased bone density [2,3]. The primary approach for management of this condition is testosterone replacement therapy. Testosterone is currently administered to hypogonadal patients using various routes including oral, parenteral (injection or implant) and transdermal delivery. Although transdermal testosterone delivery devices first became available in the 1980s, percutaneous administration of testosterone for treatment of hypogonadism was reported as early as the 1930s [4]. Transdermal delivery of testosterone offers a number of advantages compared with other routes of delivery including improved patient compliance, ease of administration and/or cessation of therapy and the achievement of sustained drug plasma levels. The goal of effective transdermal testosterone delivery is to achieve plasma levels in the range of normal endogenous production of 3–10 mg over 24 h and in a time dependent manner thus mimicking the circadian profiles of healthy males [5,6]. In this article the historical development of transdermal testosterone formulations is reviewed as well as the various formulations currently are available. Emerging technologies are also considered as well as safety considerations for steroidal hormone formulations.

Abbreviations: AUC, area under the plasma concentration time curve; C_{max}, maximum plasma concentration; C'_{ss}, time averaged steady state testosterone concentrations; DHT, dihydrotestosterone; DMAC, dimethyl acetamide; DMF, dimethyl formamide; DMSO, dimethyl sulphoxide; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MO, mineral oil; PG, propylene glycol; SHBG, sex hormone binding globulin.

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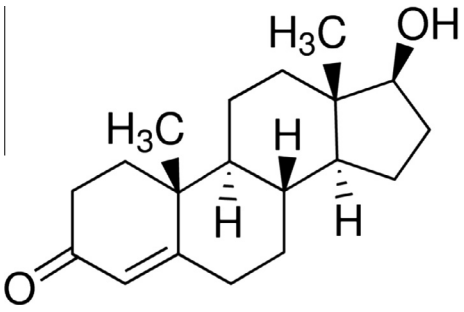

Fig. 1. Testosterone.

Table 1
Physicochemical and pharmacokinetic properties of testosterone.

Molecular weight[a]	288.4
Melting point[a]	152–157 °C
Log P [a]	3.3
Solubility[b]	0.04 mg/ml at 37 °C
Half-life [c]	10–100 min
Protein binding[d]	97–98%
Clearance[e]	1272 ± 168 l/day

[a] Moffat et al. [7].
[b] Cichon and Janick [8].
[c] Sandberg and Slaunwhite [9]; Hellman and Rosenfeld [10].
[d] AHFS Drug Information [11].
[e] Wang et al. [12].

2. Physicochemical properties, pharmacokinetics and metabolism

The physicochemical properties and pharmacokinetics of testosterone are summarised in Table 1.

When administered orally, testosterone is subject to significant metabolism in the gastrointestinal tract [13] and in the liver [14]. Following intravenous injection, the half-life of testosterone in blood has been reported to vary from 10 to 100 min [9,10]. Testosterone is metabolised to several keto derivatives via oxidation at the 17-OH group as well as to dihydrotestosterone (DHT) and estradiol. Metabolites are excreted as glucuronide or sulphate conjugates [9] with about 6% of drug being excreted unchanged [11]. In the systemic circulation testosterone is bound to sex hormone binding globulin (SHBG) tightly, and loosely to albumin with a small amount (~2%) of the free molecule [15,16]. Total testosterone measurement is accepted for evaluation of most patients; however, free testosterone is determined in some cases because of changes in SHBG concentration with health status, age or drug therapy [17].

Testosterone is metabolised in adipose tissue and skin by 5α reductase and aromatase to DHT and estradiol, respectively [18]. Higher levels of reductase are found in perianal skin areas e.g. the scrotum [19] explaining the elevated levels of DHT observed in studies with scrotal patches [20,21]. Long term exposure to testosterone has also been suggested to increase 5α reductase levels in hypogonadal men [22]. The potential long term effects of elevated DHT associated with scrotal patches raised concerns as elevated DHT levels had earlier been reported in prostate hyperplasia [23].

3. Testosterone skin permeation

Christophers and Kligman [24] reported the measurement of testosterone absorption *in vivo* using a residual analysis technique in 10 young (19–30 years) and 10 old (71–82 years) subjects. The site on the back was first cleansed with ether followed by application of 0.02 ml of a 1% solution of ^{14}C testosterone in ethylene glycol monomethyl ether over an area of ~1.8 cm^2. Silicone vacuum grease was used to ensure no spreading of the solutions and initial counts were taken after drying of the application. Following occlusion of the site with Saran Wrap for 24 h final radioactivity was measured. The difference between the initial and final counts indicated 38% absorption for younger subjects and 13% absorption for older subjects. However it should be noted that this study does not necessarily show that this high amount was absorbed into the circulation; there may be some remaining in the stratum corneum. In a later study by Roskos et al. [25], where direct measurement of testosterone was conducted, no significant differences in testosterone absorption for younger and older subjects were observed. Radiolabelled testosterone was applied to the forearm in an acetone vehicle at a dose of 4 μg/cm^2. Urinary testosterone measurements indicated that the percentage dose absorbed for the young group (22–40 years) was 19.0 ± 4.4% and for the old group the value was 16.6 ± 2.5%. Measurement of testosterone from the human forearm was also reported by Feldman and Maibach in a number of earlier studies [26,27]. Radiolabelled testosterone was dosed at 0.06 mg/13 cm^2 in an acetone vehicle containing 25% of either dimethyl formamide (DMF), dimethyl acetamide (DMAC), dimethyl sulphoxide (DMSO), mineral oil (MO) or propylene glycol (PG). Treated sites were not protected in any way and subjects were requested not to wash the areas for one day. The urine of subjects was collected for five days and analysed with 11.8% of the radiolabel being excreted for the control vehicle (acetone alone). DMSO and DMF increased the penetration of testosterone by four and two-fold, respectively. DMAC and PG also increased testosterone permeation but to a lesser extent and MO had no effect compared with the control. In a later study, conducted under similar condition, the amount of testosterone absorbed from an acetone vehicle was reported as 13% of the applied dose [28]. Schaefer et al. [29] estimated the flux of testosterone through skin as 0.05 nmol/cm^2/h over a 12–24 h period, based on the earlier work of Maibach and colleagues. The authors also determined a flux value for testosterone of 1 × nmol/cm^2/h for a 0.1% preparation based on *in vitro* experiments over 100 min; as this is a relatively short time, steady state is not likely to have been achieved.

Bucks et al. [30] reported values of ~20% of testosterone absorbed for a repeated application study in five healthy male volunteers. Testosterone was applied in an acetone vehicle over a 28 cm^2 area of the forearm at a dose of 4 μg/cm^2; radiolabelled compound was applied on days 1 and 8 while unlabelled material was applied for days 2–7 and days 9–14. The application site was washed every day prior to application of the next dose and urine was collected daily for ^{14}C analysis. In a later study [31], testosterone absorption *in vivo* was studied for occluded versus "protected" (covered but not occlusive) conditions. Following a single dose application the percentage of drug absorbed for the occluded studies was higher (46%) compared with the protected conditions (18%). For multiple doses applied at the same skin site (daily application at the same skin site for 14 days) drug absorption at day 8 was not significantly different compared with the single dose occluded study (~50%).

4. Transdermal testosterone patch formulations

4.1. Scrotal patches

Most of the matrix scrotal patches developed by Alza which were evaluated in the early clinical studies were available in three sizes: 20 cm^2, 40 cm^2 or 60 cm^2 with respective drug content being 5 mg, 10 mg and 15 mg. Approximately one-third of the drug content was delivered from the patches. Elevated levels of DHT and