Dirk Schultheiss · Dirk-Michael Hiltl
Mohammad R. Meschi · Stefan A. Machtens
Michael C. Truss · Christian G. Stief · Udo Jonas

Pilot study of the transdermal application of testosterone gel to the penile skin for the treatment of hypogonadotropic men with erectile dysfunction

Abstract Androgens influence important central and peripheral mechanisms of the erectile system. The relevance of a moderate decrease of serum testosterone level for erectile dysfunction (ED) has not been clarified so far. The aim of our study was to offer an easy transcutaneous method of androgen application. A previous study on the pharmacokinetic profile of the testosterone gel applied, showed marked elevation of the serum levels of testosterone. In our study, 46 hypogonadal patients with ED and total lack of vaginal penetration applied testosterone gel (4 mg/day; supplied by Azupharma, Germany) to the penile skin twice a day over 6–8 weeks, after a run-in period with placebo gel of 2 weeks. All patients showed decreased testosterone serum levels (<3 ng/ml) in at least two morning samples over a period of 3 weeks before treatment. Psychogenic etiology was excluded by a sexual psychologist. Patient age was 37–69 years (mean 53.5). Three patients (6.5%) responded to placebo in the run-in phase and were withdrawn from further treatment. Fifteen patients (32.6%) showed improved erection, allowing penetration and sexual intercourse. Twenty-eight patients (60.9%) did not respond to therapy. Local genital skin irritation was not observed. Elevation of peripheral testosterone was not correlated to a positive therapy response. A success-rate of 32.6% in this group of patients after exclusion of psychogenic patients and placebo-responders seems to justify further investigations. A medication period of 6–8 weeks is most probably too short to induce imaginable regenerative effects of testosterone on the erectile system. We therefore suggest that future double-blind and placebo-controlled studies should be designed for a minimum of 3 months. Testosterone gel may be a cost effective form of androgen administration.

Introduction

Permanent hormonal insufficiency, as in hypogonadal patients, was shown to induce central [10, 21, 32] and peripheral changes of the erectile system, e.g., resulting in smooth muscle degeneration of the corpus cavernosum [33]. However, the relevance of a moderate decrease of blood testosterone level in adults and aging males for erectile dysfunction (ED) and the role of androgen replacement therapy has not been elucidated so far [1, 13, 24, 25, 31].

Androgen injection therapy had been the gold standard for hormonal substitution over the last decades. More recently, several types of oral application have been used but have not found wide acceptance. Over the past few years transdermal androgen delivery patch systems, either for scrotal or nonscrotal skin, have been developed and also studied for the treatment of sexual dysfunction [1]. The transdermal method of application seems to be a physiological way of substitution by imitating the circadian androgen rhythm and avoiding peak serum levels of testosterone after injection.

The aim of our clinical pilot study was to examine the efficacy of another transcutaneous mode of testosterone application by gel formulation, in our case for patients with hypogonadism and ED. A previous study on the pharmacokinetic profile and bioavailability of this testosterone gel, as outlined below, verified marked elevation of the blood levels by proving different routes versus reference and placebo, and was the basis for our clinical pilot study.
Pharmacokinetic study

A semi-blinded bioavailability crossover-study of a new 0.85% testosterone propionate gel formulation (255 mg testosterone propionate/30 g gel) was initiated by industry (Azupharma, Germany) and performed by an independent clinical research organization (CRO). Each of 12 healthy, elderly men with serum testosterone in the lower normal range (3–5 ng/ml) were submitted to four different treatment options (a–d) over 1 day each:

a. Two doses of testosterone gel applied to the scrotal skin.
b. Two doses of testosterone gel applied to the penile skin.
c. A single dose of reference scrotal patch containing 10 mg and releasing 4 mg testosterone/day; commercial Testosterone Transdermal System (Testo-derm TTS, Alza) patch [2].
d. Two doses of placebo gel applied to the penile skin in half of the subjects and to the scrotal skin in the others.

The first dose (gel or patch) was applied at 8:00 A.M. and the second dose of gel at 4:00 pm. In the case of penile application, men were advised to retract the foreskin and apply a defined weighted amount of gel to the preputial skin. Sixteen blood samples were taken at defined intervals during the 24 h of the day of application, and skin tolerability and adverse events were registered. The results were used to define the dose of the testosterone gel comparable to the TTS patch releasing 4 mg testosterone per day (area under curve calculation).

The overall relative bioavailability of the new testosterone gel was about 50–65% of the TTS patch. In contrast, the interindividual variation of serum testosterone levels was higher with the TTS patch than with testosterone gel. Dihydrotestosterone serum levels were similar between scrotal gel and TTS patch and were slightly higher after penile application.

Owing to the fact that the patent for the described testosterone gel is still pending, the complete and detailed results of this bioavailability study are to be presented separately at a later time.

Patients and methods

In a clinical pilot study at our department, 46 patients with ED and total lack of vaginal penetration for at least 1 year were enrolled. The patients applied 1 cm of testosterone gel (1 cm gel = 250 mg gel = 2 mg testosterone propionate) to the penile skin in the above mentioned technique twice a day (≈2 × 2 mg/day) over 6–8 weeks, after a run-in period with placebo gel of 2 weeks. The clinical data of the patients (placebo-responders excluded) concerning age, median total serum-testosterone level before treatment, duration of ED, and concomitant disorders are revealed in Table 1 and Table 2. All patients showed decreased serum-testosterone levels (<3 ng/ml) in at least two morning samples over a period of 3 weeks before placebo treatment. When subdivided into three age groups (<50 years, 50–59 years and ≥60 years) no significant difference of pretherapeutic serum-testosterone level was obvious within these groups (Table 3). Psychogenic etiology was excluded by a sexual psychologist. Twelve patients had previous yohimbine therapy without success. Concomitant diseases were diabetes mellitus in six cases and a previous episode of spinal disc prolapse in five cases. Furthermore, three patients were under β-blocker medication (compare Table 1 and Table 2). Routine blood controls and serum hormonal parameters (including total testosterone, free testosterone, dihydrotestosterone, estrogen, LH, FSH and SHBG) were taken for safety control every 2 weeks. At the time of this pilot study, a validated German translation of the IIEF (International Index of Erectile Function) was not available; therefore the efficacy of the treatment with regard to the improvement of ED was evaluated by a short self-designed questionnaire.

Results

Patient age was between 37 and 69 years (mean 53.5). Only three patients (6.5%) responded to placebo medi-

<table>
<thead>
<tr>
<th>Table 1 Clinical data of responders (n = 15). ED erectile dysfunction</th>
<th>Age</th>
<th>Median total serum-testosterone before treatment (ng/ml)</th>
<th>Duration of ED (years or primary ED)</th>
<th>Concomitant disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39</td>
<td>2.9</td>
<td>8</td>
<td>Primary ED</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>2.4</td>
<td>10</td>
<td>Primary ED</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>2.9</td>
<td>4</td>
<td>Peyronie</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>2.9</td>
<td>2</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>2.9</td>
<td>4</td>
<td>Testicular hypoplasia</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>1.9</td>
<td>5</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>2.8</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>2.4</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>2.6</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>2.9</td>
<td>23</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>2.6</td>
<td>2</td>
<td>Testicular hypoplasia</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>1.8</td>
<td>4</td>
<td>Spinal disc prolapse</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>1.8</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

51.5 (39–68) 2.6 (1.8–2.9)