Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies

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TABLE OF CONTENTS
- Introduction
- Case report
- Testosterone gels
- Risk of transfer
- Risk of hyperandrogenism
- Review of case reports
- Review of unpublished studies
- Conclusions
- References

Topically applied testosterone gels are a widely used mode of testosterone replacement therapy. A concern associated with the use of testosterone gel is unintentional transfer to children or women by skin contact with the application site. We present a case of female hyperandrogenism most likely caused by transfer of testosterone gel used by her partner. Additionally, we searched the computerized database PUBMED and the FDA medical reviews for case reports and clinical trials concerning transfer risk. Several case reports and the results of clinical trials indicate that transfer of testosterone from gel-treated males to women and children is possible and clinically relevant. Thus, the potential of testosterone transfer in gel users should be recognized as a possible side effect of this form of testosterone replacement therapy.

Key words: testosterone gel / topical transfer

Introduction

Androgen replacement using topically applied testosterone gel has been proven to be convenient and effective. Once daily application of these gels to the non-scrotal skin results in relatively stable and physiological testosterone levels in most users (Steidle et al., 2003; Wang et al., 2004). A concern associated with the use of testosterone gel is unintentional transfer to children or women by skin contact with the application site. We present a case of female hyperandrogenism most likely caused by transfer of testosterone gel used by her partner.

Case report

The patient is a 31-year-old female who presented with progressive hirsutism for a period of 12 months. She had an unremarkable history, had her menarche at the age of 13 and had regular menses until the age of 26. From that age, she had been using a levonorgesteral containing IUD (Mirena) resulting in oligomenorrhea. On examination, she appeared normal, non-Cushingoid, weight 75 kg, height 1.65 m, body mass index 27.6 kg/m², blood pressure 130/85, with mild hirsutism (Ferriman and Gallwey score 9) but no clitoromegaly, temporal baldness or deepening of the voice. Laboratory evaluation
about one-third of users and have caused and easy. Testosterone patches have been widely used, but have the prevented. Unlike i.m. injections, application of a dermal gel is painless administration in that extensive first-pass metabolism in the liver is Transdermal application of testosterone offers advantages over oral administration. 

Figure 1 Plasma testosterone levels in the presented subject.-

Dotted line represents the upper limit of the female reference range. Shaded area represents the period at which Androgel® had been used by the male partner. Samples were measured using a Coat-a-Count radioimmunoassay (Diagnostics Products Corporation, Los Angeles, CA, USA); inter- and intra-assay CV are 10% and 8%, respectively, at 2 nmol/l. Cross-reactivity was below 1% for all naturally occurring steroids except for dihydrotestosterone (3.4%).

showed normal levels for TSH, random cortisol, androstenedione and DHEAS. Testosterone levels measured over a period of 3 months ranged from 1.6 to 6.7 nmol/l (Fig. 1; normal range <2.5 nmol/l). Her partner, a professional violinist, has been using AndroGel® 50 mg daily for 2 years because of primary hypogonadism after hemicastration and chemotherapy as a treatment for testicular cancer. When asked, he stated that he applied the gel to the upper arms and the abdomen in the morning, washed his hands and left for work. He said he waited at least 6 h after application of the gel before having physical contact with his partner. He was not aware of the recommendation to take a shower or cover the application sites before having physical contact. After stopping use of the gel by her partner, testosterone levels normalized, remained in the normal female range and the patient noticed that regrowth of hair, after shaving and waxing, was alleviated. However, after her partner restarted using the gel with the explicit instructions to cover the application sites, the patient’s plasma testosterone level increased again to a level of 6.6 nmol/l. This short period of re-exposure did not result in a noticeable recurrence of excess hair growth. The male partner was advised to stop using the gel and switch to injectable testosterone undecanoate, after which the patient’s plasma testosterone level normalized again.

Testosterone gels

Transdermal application of testosterone offers advantages over oral administration. In that extensive first-pass metabolism in the liver is prevented. Unlike i.m. injections, application of a dermal gel is painless and easy. Testosterone patches have been widely used, but have the disadvantage that they are visible on the skin and that the exposed skin area is relatively small. Moreover, adverse skin reactions occur in about one-third of users and have caused ~10% to discontinue this type of treatment. The allergic-type skin reactions are primarily caused by the ethanol component of the formulation, whereas skin irritation may be caused by the adhesives in the patch (Steidle et al., 2003). Testosterone gels offer an invisible and convenient mode of transdermal testosterone therapy with a much larger skin exposure, improving skin penetration and generally having better skin tolerability. To date, three testosterone gels are approved and available in Europe and/or the USA: Androgel/Testogel (Unimed), Testim (Auxilium Pharmaceuticals) and Tostren/Tostrex (ProStrakan). Testosterone gels typically consist of testosterone (1% or 2%), purified water, ethanol and polyacrylate (carbomer) as a gel-forming substance. Ethanol acts as a solvent for testosterone and as a vehicle to transport testosterone through the stratum corneum, the outer layer of the skin. The gels differ primarily by the penetration enhancers added to the gel to increase the uptake of testosterone through the skin (Table I). Although higher skin penetration may be beneficial, penetration enhancers may also lead to skin irritation (Williams and Barry, 2004). Therefore, gels may differ according to bioavailability of the applied dose and the potential to cause skin irritation. Although few head-to-head studies have been executed, the bioavailability of the different gels does not appear to be largely different, since gels achieve physiological male testosterone levels in most patients with a similar dose of applied testosterone (McNicholas et al., 2003; Wang et al., 2004). The recommended application sites are the abdomen, the shoulders and upper arms and the inner thighs. Although the large area of application of the gels enhances skin penetration and bioavailability, it also increases the risk for involuntary transfer of the applied drug by skin contact. Therefore, users are recommended to wash their hands after application of the gel, to cover the exposed skin with clothing or to take a shower prior to physical contact. Although transdermal testosterone gels are widely used, the number of reports of transfer to women and children is small. There is only one clinical trial, investigating the potential of transfer, which has been published in a peer-reviewed journal (Rolf et al., 2002). Below we will discuss this study, the case reports and unpublished studies conducted by gel manufacturers.

Table I Contents of approved testosterone gels.

<table>
<thead>
<tr>
<th>AndroGel®</th>
<th>Testim®</th>
<th>Tostrex®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>Ethanol</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Water</td>
<td>Water</td>
<td>Water</td>
</tr>
<tr>
<td>Testosterone 1%</td>
<td>Testosterone 1%</td>
<td>Testosterone 2%</td>
</tr>
<tr>
<td>Carbomer 940</td>
<td>Carbomer</td>
<td>Carbomer 1382</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>Acrylates</td>
<td>Butyl hydroxytoluene</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>Pentadecanolactone</td>
<td>Troalmine</td>
</tr>
<tr>
<td>Glycerine</td>
<td>Oleic acid</td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Isopropyl alcohol</td>
<td></td>
</tr>
<tr>
<td>Tromethamine</td>
<td>Propylene glycol</td>
<td></td>
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Risk of transfer

The recommended starting dose for the available testosterone gels is 50 or 60 mg testosterone per day. The average male testosterone production rate is estimated to be between 5 and 10 mg per day. This

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implies a bioavailability of the applied dose between 10% and 15%. This means that up to 90% of testosterone is either metabolized in the skin or remains on the surface of the skin. Rolf et al. showed that up to 8 h after application of a (currently unavailable) 2.5% hydroalcoholic testosterone gel, 60% of the administered dose could be retrieved from the application site using an alcohol containing swab (Rolf et al., 2002). The retrieval rate remained stable from 10 min after application until 8 h after application, indicating that testosterone uptake into the stratum corneum for the tested gel is limited to the first minutes after application. This indicates that a large reservoir of testosterone is left on the skin with the potential to be transferred. The limited bioavailability of testosterone has been ascribed to the fact that testosterone primarily penetrates the skin when dissolved in a vehicle such as alcohol. When applied to the skin, alcohol evaporates quickly, leaving the majority of the applied testosterone on the surface of the skin. Mazer et al. (2005) showed that significant transfer of applied testosterone takes place to clothing worn over the application site. Moreover, Rolf et al. (2002) showed that more than 3% of applied testosterone that remains on the skin after application can be readily transferred to non-exposed skin by a 5 min skin-to-skin rubbing experiment. Washing the skin 10 min after application of the gel lowered the amount of recovered testosterone from 60% to 15% and did not result in lower bioavailability of the studied gel. However, this may not be applicable to all gels since washing several hours after application of Testim resulted in almost 30% lower 24 h integrated plasma testosterone levels (http://www.fda.gov/cder/foi/nda/2002/21-454_Testim.htm).

**Risk of hyperandrogenism**

Transfer of testosterone to the skin may not necessarily result in increased levels of testosterone in the blood of exposed individuals. In men, it has been shown that bioavailability of applied testosterone is limited to 10–15%. Moreover, as shown above, it is questionable whether any of the crystalline testosterone left on the skin after application actually penetrates the skin in the absence of alcohol, knowing that the alcohol vehicle has already vaporized within minutes after application. However, knowing that plasma testosterone levels in women and children are only a few percent of those in men, even small quantities of transferred testosterone may result in detectably increased plasma levels in women and children and may potentially result in the clinical syndrome of hyperandrogenism. Rolf et al. (2002) showed that although testosterone may be transferred by intensive skin contact, this did not result in a detectable increase in plasma testosterone levels in exposed chemically castrated men. Their hypothesis to explain this phenomenon was that penetration of transferred testosterone through the skin will not occur in the absence of the already vaporized alcohol vehicle. This is the only published transfer study to date in a peer-reviewed journal. The results of this study are in contrast with our case report and others, as outlined below, and the results of unpublished testosterone gel transfer studies that can be accessed via the medical reviews of the FDA website (www.fda.gov).

**Review of case reports**

To date, 10 children have been described with precocious puberty as a result of involuntary exposure to topical androgens (Yu et al., 1999; Kunz et al., 2004; Brachet et al., 2005; Bhowmick et al., 2007). In these cases, the responsible androgen was either unknown, a 10% liposomal testosterone gel or a crème containing 4 androstenedione. In only one of these cases, the currently widely prescribed AndroGel was involved (Bhowmick et al., 2007). In this case, as in our case, the necessary precautions to prevent transfer were not taken and the child was exposed to repeated skin contact with his father without protective clothing. Moreover, the child slept in the same bed with his parents, potentially exposing him to testosterone transfer via bed sheets. More than 20 years ago, Delanoe et al. reported increased testosterone levels in 11 women whose spouses were participants in a male contraception study for which they were using Percutacrine Androgenique Forte (Laboratoires Besins-Iscovessco; 100 mg testosterone in an alcoholic solvent) (Delanoe et al., 1984). Men were advised to take a shower 10 min after application of the ointment, yet this regimen appeared ineffective in at least three cases. A recent case of hyperandrogenism in an adult woman supposedly also involved AndroGel (Merhi and Santoro, 2007). In this case, all precautionary measures to prevent transfer were taken and the only potential route via which the couple could have transferred testosterone was sharing a towel. These case reports show that topical androgens may result in clinical syndromes of hyperandrogenism in exposed children and women. Although the products described in these reports are mostly different from the currently available testosterone gels, AndroGel was responsible for at least three cases, including our case. Crémes or liposomal gels may not be comparable with hydroalcoholic gels. In hydroalcoholic gels, the solvent evaporates quickly, presumably leaving any remaining testosterone in a crystalline, inactive form on the skin. In crémes or liposomes, testosterone may remain on the skin in a dissolved and therefore active, skin penetrating form posing a higher risk once transferred to vulnerable individuals. However, these case reports show that also hydroalcoholic gels may induce clinical hyperandrogenism in involuntary exposed individuals, indicating that at least part of the testosterone reservoir on the male skin can be transferred to others and penetrate the skin under appropriate conditions. It has been speculated that testosterone may be dissolved in sweat (Delanoe et al., 1984; Mazer et al., 2005) which would explain increased testosterone levels in exposed women and children even hours after application of the gel and evaporation of the alcohol vehicle.

**Review of unpublished studies**

The potential of testosterone gel to increase testosterone levels in exposed untreated women has been studied by all manufacturers, although the results have not been published in peer-reviewed journals. Excerpts of the AndroGel and Testim studies can be found on the FDA website (www.accessdata.fda.gov/scripts/cder/drugsatfda/). Detailed results of transfer studies with Tostran are not publicly available. Studies with AndroGel and Testim show that testosterone levels may be raised in the spouses of treated men in experimental settings. In one study (UMD-98-037), males applied 100 mg of AndroGel to the upper arms, shoulders and abdomen. They were asked to have 15 min of intensive abdomen-to-abdomen skin contact with their spouses per day for a period of 7 days. The time between application of the gel and
skin contact varied from 2 to 12 h between different groups. One group of men was asked to wear a shirt covering the exposed areas during abdominal contact. The mean 24 h plasma testosterone level in the exposed women doubled after 1 day and even quadrupled after 1 week of skin contact. Mean testosterone levels in women were lower when the interval between application and skin contact was longer; however, even 12 h after application, considerable transfer of testosterone appeared to take place, indicating that transfer and uptake of transferred testosterone may take place long after application of the gel. Wearing a shirt prevented a detectable increase in testosterone levels in women. Taking a shower 1 h after application of the gel also prevented significant transfer (UMD-99-023) without significantly affecting the mean 24 h testosterone level in treated males. This shows that most applied testosterone is absorbed through the skin shortly after application. A similar study (AUX-TG-206) was conducted using Testim 100 mg applied to the abdomen with 15 min intensive skin contact 1–12 h after application. The mean 24 h testosterone level in the female partners increased up to 12 times from the baseline level. Even in the group who had skin contact 12 h after application, the mean 24 h testosterone levels in women were 8-fold over the baseline level. Wearing a shirt did not completely prevent transfer of testosterone. Applying Testim to the shoulders (AUX-TG-209) appeared to lower transfer potential significantly. Showering 1–6 h after application of the gel lowered the 24 h mean testosterone levels in treated men by 25–30% (AUX-TG-207).

From these studies, it can be concluded that both gels have the potential to raise testosterone levels in women after skin contact with treated men even hours after application. Wearing a shirt covering the application sites or taking a shower after application appears to minimize the risk of testosterone transfer.

**Conclusions**

Several case reports and the results of clinical trials indicate that transfer of testosterone from gel-treated males to women and children is possible and clinically relevant. Surprisingly, there is only one peer-reviewed publication of a clinical study addressing the risk of transfer of testosterone with a gel that is currently not available. This is the only study that does not show a significant risk of testosterone transfer. Other unpublished studies investigating commercially available testosterone gels show definite evidence for clinically relevant transfer of testosterone by skin contact. In light of the widespread use of testosterone gels and the paucity of reports on inter-person transfer, the actual risk of causing clinically relevant hyperandrogenism in contaminated women or children is probably limited. However, the potential of testosterone transfer in gel users should be recognized as a possible side effect of this form of testosterone replacement therapy.

**Conflict of interest:** The author has nothing to disclose.

**References**


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