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Editorial

Secondary exposure to testosterone from patients receiving replacement therapy with transdermal testosterone gels

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The potential for unintended transfer of testosterone to others from adult men receiving transdermal testosterone gel treatment for hypogonadism is a recognized safety concern, due to the undesirable pharmacologic effects of testosterone in women and children[1,2]. The following three papers present the results from five phase 1 studies that investigated the transfer of testosterone to adult women from male partners who applied a 1.62% testosterone gel (AndroGel 1.62%, Abbott)[3–5].

There are four gel products currently marketed in the United States for testosterone replacement therapy in hypogonadal males: AndroGel 1%, AndroGel 1.62% (Abbott, North Chicago, IL), Testim (Auxilium Pharmaceuticals, Malvern, PA), and Fortesta (Endo Pharmaceuticals, Chadds Ford, PA). In addition a 2% topical solution is available (Axiron, Lilly, Indianapolis, IN)[6]. These products are applied topically and deliver testosterone to increase serum concentrations to eugonadal levels in men with low testosterone levels. Testosterone gels are applied daily to the skin of the upper arms/shoulders and/or abdomen, or thighs of male patients, depending on their dosing instructions[7–10]. Since only a low fraction of testosterone is absorbed transdermally from the gels, there exists a significant reservoir of steroid on the surface of the skin, and this residual testosterone could be transferred to others who come into direct skin contact with the patient's site of gel application[11]. Transfer of testosterone to women or children via skin contact with the application site following gel application has been reported[12,13]. Even small quantities of testosterone transferred on a repeated basis to these individuals may result in the clinical signs and symptoms of hyperandrogenism[1], sexual precocity, or inappropriate virilization[14–16].

The signs and symptoms of secondary testosterone exposure in children include the development of pubic hair, enlargement of the penis or clitoris, increased number of erections and libido, advanced bone age, and aggressive behavior. Usually these signs regress once the testosterone source is removed, although there are instances when the genitalia do not completely return to normal size, and bone age remains slightly greater than chronological age. The signs and symptoms of testosterone exposure in women are the development of acne, changes in body hair distribution or other signs of virilization, or menstrual irregularity. Testosterone product labeling states that testosterone is teratogenic and may cause fetal harm[10]. Fetal exposure to androgens can cause virilization, so testosterone exposure should be particularly avoided during pregnancy.

The United States Food and Drug Administration (FDA) addressed the issue of testosterone gel safety in May 2009. It reported the receipt of eight reports of secondary exposure to testosterone in children ranging in age from 9 months

to 5 years. The FDA noted that, in most of the cases, patients had failed to follow the appropriate use instructions, resulting in direct contact between the site of gel application and the child. The FDA now requires that product labeling for topically administered testosterone products include a boxed warning on secondary exposure to testosterone stating that virilization has been reported in children who were secondarily exposed to topical testosterone products, children should avoid contact with unwashed or unclothed application sites in men using the testosterone product, and healthcare providers should advise patients to strictly adhere to recommended instructions for use[12,17]. The FDA also requires the manufacturers of these products to develop a Medication Guide as part of a Risk Evaluation and Mitigation Strategy[18].

Although all of the currently approved product labels for testosterone gel formulations summarize the transfer studies that have been performed during the development and registration process, most have yet to be published outside of product-specific labeling and the existing literature is limited[11,19,20]. In these studies, adult women had contact with the site of drug application on their male partners, and their serum testosterone concentrations were then measured at prespecified time intervals to determine transfer and systemic absorption of testosterone.

It is difficult to directly compare these results across testosterone formulations, as the studies to evaluate transfer differ in the sites of application, the quantity of testosterone applied, and the precise methodology, but total testosterone level C_{max} increased from more than two times to at least four times, when compared with baseline. When the site of application was covered with clothing, transfer was either prevented or reduced.

Two of the following papers present data from four different transfer studies between men who applied AndroGel 1.62% and their female partners. These studies demonstrate that after abdominal skin contact, female testosterone exposure increased 0.27 to 2.8 times compared with baseline[3,4]. Covering the application sites with a t-shirt mitigated transfer to the female partners when the highest dose (5.0 g of gel; 81 mg testosterone) was applied to the upper arms and shoulders, or the 2.5-g (40.5 mg testosterone) dose was applied to the abdomen. However, if the 81-mg dose was applied solely to the abdomen, a t-shirt would only reduce transfer by approximately 40% to 48%.

Washing the application site also may prevent or reduce testosterone transfer[21]. Two of the following reports present data that shed light on this issue[3,5]. These reports show that applying 81 mg of testosterone (5 g of gel) and then washing (showering) the application site 2 hours after dosing reduced the transfer of testosterone such that the C_{av} in the females was comparable to baseline and the C_{max} was just slightly higher at 14%. Washing as soon as 2 hours after dose administration reduced the amount of testosterone on the male skin by at least 81% and had little impact on bioavailability to the male subjects enrolled in the study.

The question of how relevant these male–female transfer studies are to adult male–child transfer, which according to the FDA, constitutes 40% (10/24) of the postmarketing cases of secondary testosterone exposure, remains unanswered. Transfer studies have not been performed on children for ethical reasons, and one would have to speculate to suggest any conclusions. Infants have increased skin permeability, and infants, as well as children, have overall smaller skin surface areas than adults, which increases the percentage of affected skin in instances of transfer to these individuals. Therefore, children may show increased testosterone absorption, due to these factors, for any isolated instance of transfer. One can speculate that if a child was exposed to a single instance of testosterone transfer from an adult male, the resulting increase in serum testosterone levels would most likely be transient and would return to baseline levels over the next 48 hours, in a manner similar to that found in healthy adult females, due to the sex steroid clearance pharmacodynamics noted in children[22]. Further, how long testosterone levels have to be elevated to produce clinical symptoms of virilization has not been fully elucidated.

It should be noted that these studies are surrogates for the transfer potential of testosterone under experimental conditions. For example, in the Stahlman and colleagues study[3], the male and female partners continuously rubbed their abdomens together for 15 minutes while held together with a waistband to ensure maximum contact. This kind of contact is unlikely to reflect real life situations, and the amount of testosterone transfer from 'realistic' extended contact or from brief, casual contact has not been characterized. There is also the possibility that testosterone gel users will not follow correct procedures as described in the label.

If secondary exposure to a partner or child is suspected, then the use of the gel should be discontinued and the cause of the exposure identified. To reduce the chances of unwanted exposure, children should avoid contact with unwashed or unclothed application sites in men using transdermal testosterone products (as well as such items as shirts or other fabric, such as towels and sheets), and healthcare providers should advise patients to strictly adhere to the recommended instructions for use.

Transparency

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Declaration of financial/other relationships
T.L.Z. and M.G.M. are employed by Abbott and own Abbott stock. A.D.R. has been on a scientific advisory board for Global Stevia Institute, has consulted for Abbott, Ipsen/Tercica, Insmed, and NovoNordisk, has received payment for the development of educational presentations from Scherer and UpToDate, and has stock or stock options in Insmed.

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