Skin hypersensitivity reactions to transdermal therapeutic systems – still an important clinical problem

Skórne reakcje nadwrażliwości wywołane przezskórnymi systemami terapeutycznymi – nadal aktualny problem kliniczny

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Summary

Transdermal therapeutic systems (TTS) belong to the widely used methods of drug administration, which allow rate-controlled drug delivery and avoidance of first-pass metabolism in the liver. Beside scopolamine, nitroglycerin (glyceryl trinitrate), nicotine, clonidine and fentanyl, also transdermal delivery of sex steroids for hormone replacement therapy and contraception is a well-known and popular method in daily clinical practice. It is estimated that approximately 20% of patients using transdermal estradiol may complain of adverse cutaneous side effects. Most of those reactions are mild or moderate, usually limited to the area of drug application. However, prolonged use may increase the chance of developing sensitization.

The purpose of this review is to provide up-to date information on the spectrum of cutaneous reactions caused by TTS and the characteristics of potential contact allergens, including sex hormones. Proper management and prophylactic measures were also included.

Key words: **transdermal therapeutic systems** / **estradiol** / **patch testing** / / **allergic contact dermatitis** /

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Strzeszcenia

Przezskórne systemy terapeutyczne (TTS) są szeroko stosowaną metodą podawania leków, która pozwala w sposób kontrolowany, ze stałą szybkością uwolnić substancję leczniczą i uniknąć efektu pierwszego przejścia w wątrobie. Oprócz skopolaminy, nitrogliceryny (trójazotanu glicerolu), nikotyny, klonidyny i fentanylu, uznaną i popularną metodą w codziennej praktyce klinicznej jest wykorzystanie przezskórnych systemów do podawania hormonów płciowych stosowanych w hormonalnej terapii zastępczej i antykoncepcji. Szacuje się, że około 20% pacjentów stosujących przezskórne systemy zawierające estradiol może skarżyć się na niekorzystne skutki uboczne dotyczące skóry. Większość z tych reakcji jest łagodna lub umiarkowana i zwykle ograniczona do miejsca aplikacji leku. Jednak długotrwałe stosowanie TTS może zwiększyć w przyszłości prawdopodobieństwo rozwoju uczulenia.

Celem niniejszego doniesienia jest dostarczenie aktualnych informacji na temat spektrum możliwych reakcji skórnych spowodowanych stosowaniem TTS oraz charakterystyka alergenów kontaktowych, z uwzględnieniem hormonów płciowych. W pracy przedstawiono ponadto ogólne zasady postępowania w przypadku pojawienia się zmian skórnych oraz działania profilaktyczne.

Słówa kluczowe: **przezskórne systemy terapeutyczne** / **estradiol** / **testy płatkowe** / / **alergiczne kontaktowe zapalenie skóry** /

Introduction

Transdermal therapeutic systems (TTS) are characterized by adhesive-containing systems, with a defined surface area, that deliver drug to skin at a controlled rate. Each TTS has three main components:

- active medication,
- adhesive material,
- enhancing agents.

Several types of TTS are currently available, and they include matrix, local-action transcutaneous, and reservoir TTSs. Matrix TTS is considered the most common type and contains a single-layer mixture of adhesive, active ingredient and other components, that is directly adjacent to the skin surface. So-called local-action transcutaneous TTS is used to deliver nonsteroidal anti-inflammatory drugs (NSAIDs) through the skin and it is similar to the matrix TTS, except a nonwoven polyester backing supporting NSAIDs formulation. A reservoir TTS is composed of a depot of liquid containing an active ingredient, attributed with permeation enhancer, which is released through a rate-controlling membrane [1].

Newer methods of drug delivery through the skin include also: programmable battery-powered carbon nanotube membrane TTS and transdermal microneedle TTS [2, 3, 4].

Characteristics of possible hypersensitivity reactions to TTS

Irritant contact dermatitis (ICD) is defined as an inflammatory reaction to various external agents with an activation of various inflammatory and immunologic mediators, however with no involvement of memory T cells or antigen-specific immunoglobulins.

ICD is usually described as a transient, mild or moderate type of reaction. An exact prevalence of ICD is unknown, however is considered to be the most common cutaneous reaction among TTS users and estimated to be present in up to 97% of subjects [3, 4].

Clinical picture of ICD includes sharply demarcated erythema, vesicles and scaling, usually with concomitant pruritus, burning or stinging sensation. ICD is most commonly reported with reservoir TTSs. Most irritant reactions are localized to the site of application and resolve spontaneously within several days of TTS removal – this is often described as a "decrescendo" reaction pattern [2].

Ingredients commonly implicated in ICD include ethanol and glycerin. Bacterial degradation of nitroglycerin may result in production of acrylic aldehyde, which is also another known irritant. TTS delivery systems are designed to be applied to the skin for prolonged periods of time. Taking this fact into consideration, sweat accumulation is thought to be one of the major factors in skin irritation with long-term applications of TTSs. Skin occlusion can lead to the obstruction of sweat ducts with subsequent escape of sweat from the duct within the skin resulting in inflammation and pruritus. Yeast and bacteria growth may additionally be promoted in the moist high-temperature environment and can also play a minor role in ICD from TTS. Another possible additional irritant is friction from the repeated removal of the patch. It has to be emphasized, that most patients continue to use the TTS despite described skin problems [6-9]. In some cases vasodilatation can mimic irritation. Swedish researchers described a patient presenting with erythema and pruritus after the application of a nicotine TTS. Patch testing revealed erythematous reaction to nicotine but with no papules, edema, or vesicles – what could be due not to contact allergy, but rather to vasodilatation which is a known effect of nicotine [10, 11].

Allergic contact dermatitis (ACD) is on the other hand a relatively rare phenomenon and regards only selected number of patients. ACD represents a type IV cell-mediated hypersensitivity reaction (delayed type hypersensitivity) according to the classification of Gell and Coombs [12, 13, 14]. Occlusive character of TTS and its irritant capacity provides an optimal environment for sensitization and moreover, prolonged use of a

patch increases the chance of developing contact sensitization. The first phase of the type IV reaction is a sensitization phase - a 7- to 14-day process that must occur prior to the development of cutaneous allergy. Once the allergic reactivity is established, the second phase is elicitation - re-exposure to contact allergen leads to ACD within hours to days at sites of recent TTS application. ACD has been reported in up to 25% of clonidine TTS users, up to 3% in nicotine TTS trials, and up to 10% with scopolamine TTS use. The reaction has also been described in case reports with the use of nitroglycerin, testosterone, estradiol, and fentanyl TTSs [3, 15-17].

Symptoms of ACD may appear even after many years of continuous exposure to the patch. Potential allergens in a TTS include the adhesive, the membrane, the solvent, the enhancer, and an active medication. ACD presents with intense erythema, pruritic inflammatory papules and vesicles (which may then rupture producing erosions). In some patients secondary dissemination of skin lesions is possible, which is called 'secondary allergisation'. ACD may be complicated by the development of postinflammatory hyperpigmentation and secondary superinfection with bacteria. Natural course of ACD is characterized by complete resolution once responsible allergen has been removed from contact with the skin. Unlike in ICD patients, ACD typically shows a "crescendo" pattern: skin reaction tends to worsen in the days after TTS removal and may then persist for over three weeks. Furthermore, a re-exposure to an allergen at a new localization may result in a flare of dermatitis at the previous site, in addition to ACD at the new site [3].

Other potential contact allergens included in TTS apart of an active medication include:

- peppermint and menthol: peppermint and menthol may be added to TTS due to their anesthetic properties and also to enhance dilation of the vessels and subsequent drug penetration [18]. It has to be emphasized, that menthol is considered a rare sensitizer but is likely to undergo metabolism to menthone, which then may induce contact sensitization.

- hydroxypropyl cellulose: pruritus, erythema, edema, and postinflammatory hyperpigmentation have been described at sites where an estradiol TTS containing hydroxypropyl cellulose, estradiol, and alcohol was applied. Subsequent allergological testing with mentioned components revealed positive results for hydroxypropyl cellulose in 70% ethanol and hydroxypropyl cellulose in mineral oil and negative results for 70% ethanol, mineral oil, and hydroxypropyl cellulose in water. Described patient presented with a negative result for hydroxypropyl cellulose in water, and that is why in authors' opinion vehicle seems important for allergen penetration and potential sensitization [19].

- ethanol: generally, ethanol is considered as a potent irritant, but ethanol contact allergy is rare and often misdiagnosed. Patients who are topically sensitized to ethanol may develop local and generalized dermatitis as a result of consumption of alcoholic beverages. There are reports on patients, who were using estradiol TTSs to treat menstrual headaches and who presented with pruritic erythematous lesions at TTS application sites. Patch testing revealed positive results ethanol, TTS with ethanol and no estradiol, TTS with ethanol and estradiol, and hydroxypropyl cellulose in ethanol. Occlusion may have promoted the sensitization [20-24].

- adhesives: there are several publications, implicating adhesives as contact allergens; in most cases, patch testing served as a helpful tool in identification of the suspected substance [25-27].

The diagnosis of ACD may be confirmed by identifying the causative allergen with the use of patch testing. Patch testing involves occlusion of various diluted allergens on the skin of the back for 48 hours. After patch test removal, the patient has to return also 24 hours later for a second reading. In some cases additional reading may be advised (96 hours and 7 days after testing). A positive reaction is defined as edematous, erythematous and possibly vesicular plaque at the site of allergen application [3, 12, 13].

Other types of reactions

Allergic contact urticaria (ACU) is an important, although rare possible reaction to TTS. ACU represents type I hypersensitivity reaction according to Gell and Coombs [14], with IgE-mediated inflammatory response to a specific allergen. This type of immediate reaction occurs within minutes of application of an allergen and clinically presents as wheals and concomitant marked pruritus. Generalized urticaria, angioedema, and even anaphylaxis may develop. ACU has been mainly described with the use of nicotine or nitroglycerin TTS. Diagnostic procedures in ACU include prick testing: Morrow-Brown lancet is used to prick through a drop of diluted suspected allergen into the dermis. Positive reaction occurs within 15-20 minutes and is defined as a wheal of a diameter at least equal to the size of positive histamine control wheal. Some individuals also present symptoms of dermatographism, a condition in which pressure or friction against the skin may produce urticarial (usually linear) response. Predisposed patients may develop a dermatographic response from the pressure of an adhesive patch and/or from the friction that occurs during removal of the patch or dressing [3].

Hypersensitivity to estrogen in TTS – review of literature data

Koch presented a 50-year-old postmenopausal woman with a history of discoid indurated erythema at a site of patch containing 5 mg estradiol and 15mg norethisterone. Itchy skin lesions appeared on third application and then progressed into bullae. Due to the reaction, patient was transitioned to an estradiol-containing gel, which also resulted in local acute eczematous eruption. Patient was patch tested with separate components of the TTS (in 1% concentration in ethanol) and gel. Diagnostics revealed strongly positive reaction to both hormones contained in TTS [28]. Similar case description provide Corazza et al., who reported on a 47-year-old, postmenopausal woman who had eczematous reaction after use of estradiol in TTS as well as gel application. What is more, patient also developed systemic pruritic eruption after switching her to oral estrogen therapy. In this case type IV of allergic reaction to transdermal estradiol and gel were confirmed in patch tests, also the verification of systemic contact dermatitis was performed [29]. Another case of systemic sensitization to 17 beta-estradiol induced by transcutaneous application was introduced by El Sayed et al. [30]. Alfaya et al. reported a case of 20-year-old woman with contact allergy to TTS contraceptives containing ethinylestradiol and norelgestromin after using them for 2 months. As an alternative, oral therapy was

offered with a good tolerance [31]. Contact dermatitis reaction was also detected in 15-year-old adolescent, who used transdermal patch as a contraceptive and after 5 months developed intensely inflammatory reaction within the site of application. However, allergic background was not confirmed in patch test [32].

On the other hand, Boehncke et al. described a woman treated initially with oral estradiol without any skin changes and then patient was switched to estradiol in TTS, what provoked the eczema. The erythema within the site of plaster application was visible on the ninth day of therapy and then evolved into formation of generalized urticarial lesions. Patient was patch tested and positive reactions to estradiol-17 beta 1%, 2% and 4% in ethanol were recorded [33].

Most of the presented literature data concern ACD to estradiol, but there are also reports on the reaction to the adhesive and to the component of the reservoir (hydroxypropyl cellulose component) [19, 34]. The possibility of cross-reactions between hydroxypropyl cellulose and the ingredient of acyclovir cream were also observed and should be taken into consideration [35]. Researchers from UK indicate also the potential of cross-reactions between sex steroids and topical glucocorticosteroids. They present a case of 61-year-old woman with chronic hand and food dermatitis and concomitant allergy to estradiol and norethisterone and numerous topical steroids [36].

Recently, systemic photosensitivity due to contraceptive patch was described. Gomez-Bernal et al. presented a case report of a 35-year-old woman who developed 3 episodes of a prurigionous papulovesicular eruption during the 3-year long use of ethinyloestradiol and norelgestromin. Discontinuation of contraceptive TTS was advised and 3 months later oral contraceptives were prescribed, which also provoked skin symptoms. Photobiological examination confirmed systemic photosensitivity [37]. To diagnose photosensitivity reaction photopatch tests are a very useful method [38].

The problem of adverse skin reactions to transdermal estradiol are mainly accentuated in warm humid climates. In a study from Mexico, 45 patients were investigated in regards of potential side effects during the use of TTS and 22,2% discontinued the therapy because of severe skin reactions characterized mostly as eczematous skin lesions associated with persistent itching [38]. Frenkel et al. provide data from Israel, in which severe skin reactions mainly in the form of erythema were noticed and led to withdrawal of treatment in 17,5% cases [40]. In both studies patch tests were not performed [39, 40].

Management and prevention of TTS cutaneous hypersensitivity

The patient should be informed that mild to moderate erythema may be observed at the time of TTS removal and has already been reported in various clinical studies. If ICD is suspected, usually use of emollients may provide temporary relief at previous patch application sites. If the severity of ICD is high and the reaction is unresponsive to emollients, twice-daily application of a low-potency topical glucocorticosteroid is advisable, however continuous application of glucocorticosteroid preparation at the same site without resolution for more than three weeks should be avoided.

As in other potential drug hypersensitivity reactions, also in suspected hypersensitivity to TTS a detailed history is the main point of the management. If a TTS-related ACD is suspected, discontinuation of treatment is the most important element of reaction management. After discontinuation, treatment with a medium-strength to potent topical glucocorticosteroid ointment applied twice daily is usually sufficient. Oral antihistamines help to alleviate pruritus. The patient should be referred to a dermatologist for consultation and patch testing after ACD resolves [2, 3, 5, 8].

The patient has to follow manufacturers' recommendations regarding site of application as it is crucial for effectiveness of the medication. However, alternating application sites is one of the most important preventive measures against TTS hypersensitivity. It is best to develop a rotational system for the area of patch application.

Another significant element is maintenance of the skin barrier function and avoidance of irritants. Proper and skin care is needed: baths and showers should be limited to 5-10 minutes and emollients should be used for bathing and after-bath regular skin moisturization. Due to well-known potential for irritation and disturbance of skin barrier isopropyl alcohol and acetone should not be used for wiping the skin. Patches should be removed gently, and scrubbing of the site to remove any residual adhesive should be avoided. An oil-based product (petroleum jelly, mineral oil) can be used to loosen any residual adhesive. One of the possible preventive measures against contact sensitization to TTS is a co-administration of topical glucocorticosteroids. Pre-medication with a glucocorticosteroid preparation has been shown to lessen the incidence and severity of skin irritation.

However, well-known adverse effects of long term topical corticosteroid administration may limit this strategy. That is why improving predictive testing for the potential development of cutaneous hypersensitivity to drugs and other components of TTS is undoubtedly an important task for the research groups worldwide [2, 3, 5, 8, 41-43].

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