

Cutaneous Reactions to Transdermal Therapeutic Systems

Andrea L. Musel and Erin M. Warshaw

Transdermal therapeutic systems have been increasingly used in the past two decades. However, cutaneous side effects are fairly common and may result in poor patient compliance. This review article summarizes the spectrum of reactions due to transdermal therapeutic systems and provides a current list of known allergens.

OVER THE LAST DECADE, transdermal administration has become an increasingly popular method of drug delivery because its benefits include not only convenience for patients but also increased compliance. Transdermal therapeutic systems allow drugs to be delivered in a rate-controlled manner, avoiding first-pass metabolism and the fluctuating plasma concentrations encountered with oral medications.¹ In most cases, there are fewer side effects than there are with oral delivery of drugs, but skin reactions are not uncommon and may compromise compliance. The purpose of this review is to provide information on the spectrum of reactions caused by transdermal therapeutic systems and to review known responsible allergens.

Types of Transdermal Therapeutic Systems

Transdermal therapeutic systems (TTSs), commonly called "patches," generally consist of three parts: an adhesive, an active pharmaceutical drug, and enhancing agents. A number of types of TTS are currently available; these include reservoir, matrix, and local-action transcutaneous patches, all of which are discussed in this article. Reservoir TTSs have a depot where liquid containing the active ingredient is stored for release through a rate-controlling membrane (Fig 1). In a matrix TTS, a mixture of the active ingredient, an adhesive, and other components is contained in a single layer that is directly adjacent to the skin; a rate-controlling membrane is not necessary (Fig 2). A local-action transcutaneous (LAT) patch is used to deliver nonsteroidal anti-inflammatory drugs (NSAIDs) through the skin. It is similar to a matrix TTS, except that it includes a nonwoven polyester backing that supports an NSAID formulation.²

Drugs commonly delivered through TTSs include testosterone, estradiol, scopolamine, clonidine, nicotine, nitroglycerin, fentanyl, lidocaine, and birth control preparations.³

Irritant Reactions to TTSs

Skin irritation is the most commonly reported cutaneous side effect among users of TTSs. The exact prevalence of irritant reactions to TTSs is unknown, but general "skin reactions" from studies involving various TTSs have been reported in up to 97% of patients.

Classic irritant reactions are sharply demarcated and are limited to the area of TTS application.⁴ Irritant reactions are most commonly reported with reservoir TTSs and usually fade quickly after removal of the patch.⁵ Ingredients that are often implicated in irritant reactions include ethanol and glycerin. Bacterial degradation of nitroglycerin can also produce acrylic aldehyde, which is another known irritant.^{4,6} Sweat accumulation is thought to be the major factor in skin irritation with long-term applications of TTSs because skin occlusion can lead to the obstruction of sweat ducts. When this occurs, sweat may escape from the duct wall and induce intraepidermal inflammation, often resulting in pruritus.⁷ In addition, yeast and bacteria growth may be promoted in the moist high-temperature environment and can also play minor roles in irritant reactions.⁸ Friction from the removal of TTSs also functions as a major irritant.

Vasodilatation can mimic irritation. Von Bahr and Wahlberg⁹ reported on a woman with erythema and itching after the application of a nicotine TTS. Upon patch testing, the patient had erythematous reactions to nicotine but no papules, edema, or vesicles. The authors concluded that the erythematous effect in this case was not due to allergy or irritation but rather to vasodilatation, a known effect of nicotine.^{9,10}

Many studies evaluating the clinical efficacy of various TTSs report cutaneous side effects but do not describe

From the University of Minnesota School of Medicine, Minneapolis, MN, and the Minneapolis Veterans Affairs Medical Center, Minneapolis, MN.

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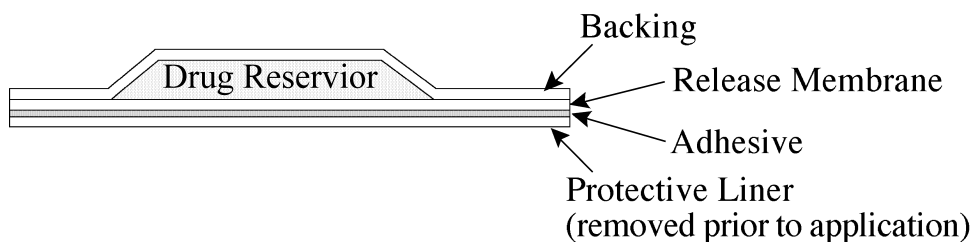


Figure 1. Cross section of a reservoir transdermal therapeutic system.

reactions in detail. Because patch-test results were not reported in the majority of cases, such side effects are considered irritant reactions for the purposes of this review; they are summarized in Table 1. Fischer and Tyler reported two cases of irritant contact dermatitis due to nitroglycerin TTSs. One patient was a 64-year-old man who presented with burning, pruritus, and erythema that was clearly demarcated and corresponded to the shape of the TTS. He had been applying TTSs in the same general area for 6 weeks. The other patient was a 55-year-old man who presented with erythema, burning, itching, and scaling on the left chest wall, where he had been applying nitroglycerin TTSs for 9 months. He had been replacing the patch every 48 hours as directed by his physician (instead of the usually recommended replacement schedule of every 24 hours) and had also been placing it in the same general area. Neither patient was patch-tested, because their reactions were clinically consistent with irritant contact dermatitis. The authors suggested that the application of patches in the same location and for longer than recommended may be a risk factor for irritant contact dermatitis.¹¹

Importance of Delivery Systems in Causing Cutaneous Reactions

The likelihood of reactions to a TTS may depend on the type of delivery system. Jordan performed an open-label crossover study that compared skin reactions to a scrotal

testosterone TTS (which clings to the skin when warmed by body heat and does not contain adhesives or permeation enhancers) and a nonscrotal testosterone TTS (which uses adhesives and permeation enhancers). Sixty subjects reported no contact allergy during use of the scrotal TTS whereas seven (12%) of the patients experienced allergic skin reactions when using the nonscrotal system, which was applied on rotating sites on the back or upper arm. Allergy was diagnosed clinically by the presence of pruritus, induration, and erythema with infiltration, along with skin "recall" reactions at previous application sites.¹² Four of these seven patients were changed to the scrotal system. None of these four patients experienced a reaction; thus, it was hypothesized that testosterone was not the sensitizer. However, formal patch testing was not performed. Compounds in the regular TTS, but not the scrotal TTS, included permeation enhancers (alcohol, glycerin, glycerol monooleate, and methyl laurate gelled with acrylic acid copolymer) and acrylic adhesives.¹²

In a randomized placebo-controlled crossover study of 82 women, Ross and colleagues found that reservoir estradiol TTSs caused more irritation than matrix estradiol TTSs. Seventy-two women completed the study. Nine (13%) discontinued using both reservoir and matrix TTSs because of skin reactions. Twenty-six patients (36%) discontinued the reservoir TTS whereas only 4 patients (6%) discontinued the matrix TTS. Patch testing was not performed.¹³ Batta and Foulds speculated that this study's

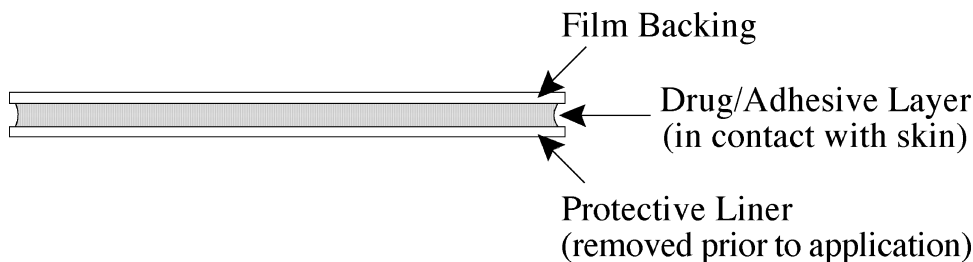


Figure 2. Cross section of a matrix transdermal therapeutic system (TTS). The matrix TTS film backing is a plastic derivative; the local-action transcutaneous TTS film backing is a nonwoven polyester.

Table 1. Irritant Cutaneous Reactions to Transdermal Therapeutic Systems

Study	Study Type	TTS	Total No. of Patients	Time Period	Patients with Cutaneous Side Effects (n = No. of Patients)	Patients Discontinued Owing to Side Effects
Weber ⁷⁰	O	Clonidine	101	12 wk	8	5
Fillingim ⁷⁸	O	Clonidine	41	88 wk	15	2
Dick ⁷⁹	O	Clonidine	15	8–20 wk	4	4
Vaillant ⁸⁰	P	Nitroglycerin	33	1–103 wk	5	0
Kounis ²⁴	NR	Nitroglycerin	320	NR	21 (6.5%)*	11 (3.4%)
Homick ⁸¹	DBX	Scopolamine	11	Four 72 h applications	≈ 3†	NR
Place ⁸²	RDB	Estradiol	124	8 wk	n NR; 20% of study weeks had SE reported	Active: 1 Placebo: 12
de Cetina ⁸³	O	Estradiol	45	24 wk	35	10
Mulligan ⁸⁴	DBPC	Nicotine	80	24 wk	Active: 11 Placebo: 5	NR
Abelin ⁸⁵	RDBPC	Nicotine	Active: 100 Placebo: 99	12 wk	Active: erythema, 25; pruritus, 29 Placebo: erythema, 13; pruritus, 8	Active: 5
Rose ⁸⁶	RDB	Nicotine	Active: 33 Placebo: 32	3 wk	Active: 32 (97%) with “at least a mild reaction,” 2 with generalized rash Placebo: 6 (19%) with “at least a mild reaction”	Active: 3 (9.1%) Placebo: 17 (53.1%)
Abelin ⁸⁷	RDBPC field study	Nicotine	Active: 156 Placebo: 155	12 wk	Active: intense erythema ± edema, 12; mild/moderate erythema, 25; pruritus, 29 Placebo: mild/moderate erythema, 14; pruritus, 8	9
Transdermal Nicotine Study Group ⁶⁶	RDBPC	Nicotine	Active: 664 Placebo: 271	6–12 wk	Active: itching or burning, 332 (50%); erythema, 93 (14%) Placebo: itching or burning, 35 (13%)	NR
Hurt ⁸⁸	RDBPC	Nicotine	Active: 31 Placebo: 31	6 wk	Active: vesicles, 2; erythema, 29 Placebo: erythema, 10	Active: 0 Placebo: 2

continued

Table 1. Continued

Study	Study Type	TTS	Total No. of Patients	Time Period	Patients with Cutaneous Side Effects (n = No. of Patients)	Patients Discontinued Owing to Side Effects
Kornitzer ⁸⁹	DBPC	Nicotine	Active: 299 Placebo: 75	24 wk	Active [‡] : edema, 3; pruritus, 16; erythema, 19 Placebo [‡] : edema, 1; pruritus, 1; erythema, 2	NR
Daughton ⁹⁰	—	Nicotine	Active: 110 Placebo: 55	4 wk	Active: 1 with TTS worn 24 h, 3 with TTS worn only while awake Placebo: 1	Active: 2 [§] Placebo: 2
Jordan ⁴¹	O (ph 1), RDB (ph 2)	Nicotine	186	Phase 1: 6 wk	Phase 1: papules + pustules, < 5.5 (< 3%); erythema, 167; pruritus, 145 tingling, 2; soreness, 2; stinging, 1; burning, 18	—
Eichelberg ⁴²	O	Nicotine	183	Phase 2: 4 d	Phase 2: papules + pustules, < 1.86 (< 1%); other than erythema, < 3.72 (< 2%)	
Jordan ¹²	OX	Testosterone	60	8 wk	Pruritus, 29; erythema, 18	6
Ross ¹³	RPC X	Estradiol	72	4 wk 16 wk	0% scrotal system; 12% nonscrotal system Matrix TTS, 6; Reservoir TTS, 35; Both, 17	NR Matrix: 26; reservoir, 4; both, 9
Gammaioni ⁹¹	O	Lidocaine	20	3 d	Slight to moderate erythema, 18; edema, 1	NR
Gammaioni ⁹²	O	Lidocaine	20	3 d	Erythema, 13	0
Barbano ⁹³	O	Lidocaine	56	3–8 wk	Burning, 5; papular rash, 1; photosensitivity reaction, 1	2
Meier ⁹⁴	RPC X	Lidocaine	40	3 wk	Active: rash, 10; pruritus, 4; vesicobullous rash, 1 Placebo: rash, 11; pruritus, 5; vesicobullous rash, 1	Active: 1 Placebo: 0

DB = double-blind; NR = not reported; O = open label; P = prospective; PC = placebo controlled; ph = phase; R = randomized; SE = side effects; TTS = transdermal therapeutic system; wk = weeks; X = crossover.

*Patch testing performed on at least 17 patients (exact number not reported).

[†]Cutaneous side effects reported in bar graph only (not numerically in text).

[‡]Reported as a 3-month cumulative incidence rate.

[§]Not reported whether due to cutaneous side effects.

patients, all of whom had previously discontinued the use of the reservoir TTS, had already been sensitized to one or more of the components of the TTS. The matrix TTS contained different ingredients to which the patients had not previously been exposed, except for estradiol, which is not a common sensitizer.¹⁴ Thus, the results of this study may not be applicable to patients who have never used an estradiol TTS.

Other Cutaneous Reactions to TTSs

Murray reported a man who developed a second-degree burn under his nitroglycerin TTS while he was sitting near a microwave in use. The TTS contained aluminized plastic to prevent volatile nitroglycerin from escaping. The aluminum portion of the TTS was heated by microwaves that apparently escaped the oven.¹⁵

Allergic Contact Dermatitis to TTSs

TTSs are ideally suited to produce sensitization because they simulate Kligman's maximization procedure, which requires occlusion, irritation, and repeated placement of the allergen at the same skin location.¹⁶ The prevalence of allergic contact dermatitis from TTSs is unknown. Sensitization may develop owing to the active pharmaceutical agent, adhesive, or other components (Table 2). Figures 3 and 4 depict areas on a woman with allergic contact dermatitis from a component of a reservoir TTS.

Active Pharmaceutical TTS Agents That Can Cause Allergic Contact Dermatitis

Clonidine

Clonidine is a centrally acting antihypertensive that can be successfully delivered transdermally. Clonidine patches are generally left in place for 7 days, which is a longer application period than is required by most other TTSs and may explain the relatively high incidence of allergic contact dermatitis from clonidine TTS.¹⁷ Although clonidine itself is a very weak sensitizer, it is the main sensitizer in the clonidine TTS, and patch tests with the nonactive components of the clonidine TTS have rarely produced reactions.¹⁷

Groth and colleagues observed 29 patients who applied clonidine TTSs to their upper outer arms; 11 (38%) of these patients experienced a local skin reaction. Patch testing with all components of the clonidine TTS was performed on 7 of these 11 patients, and 6 of these 7 were found to be allergic to clonidine.¹⁸ Horning and colleagues conducted a 2-year prospective study with 20 patients to determine the

Table 2. Transdermal Therapeutic System Components and Recommended Patch-Test Concentrations

<i>TTS Component</i>	<i>Recommended Patch-Test Concentrations</i>
<i>Adhesive components</i>	
Silicone adhesive	NR
Acrylic adhesive	NR
Polyisobutylene ³⁵	1% benzene 2% benzene
Mineral oil ⁸⁷	As is
<i>Active ingredients</i>	
Estradiol-17 β ⁵⁹	1% pet 5% pet
Clonidine ^{1,95}	0.9% pet 9% pet
Fentanyl	NR
Flurbiprofen ⁵²	2% pet
Hydroxyprogesterone ^{33,34}	1% in 90% eth
Mesterolone ³⁴	1% aq
Nicotine ^{9,42,43}	10% aq
Nitroglycerin ^{21,25,63}	0.2% pet 0.5% pet 1% pet 2% pet 3% pet 0.2% aq
Progesterone ³⁴	1% in 90% eth 1% aq
Scopolamine ^{29,59}	1% aq 1% pet 2% pet
Testosterone enanthate ^{33,34}	1% in 90% eth 2.5% in oil
Testosterone propionate ^{33,34}	1% aq 1% in 90% eth 2.5% in oil
Testosterone undecanoate ³¹	1% in 90% eth 4% in oil
<i>Other components</i>	
Acrylate ⁵⁹	0.1% pet 1% pet
Acrylic acid ⁵⁹	0.1% pet
Anhydrous colloidal silicon dioxide	NR
Brown ink	NR
Carrageen ^{42,59}	As is
Colloidal silicone fluid	NR
Copolymer foam	NR
Ethanol USP ^{54-56,59}	10% aq 70-95% aq As is
Ethylene vinyl acetate copolymer	NR

continued

Table 2. Continued

TTS Component	Recommended Patch-Test Concentrations
<i>Other components</i>	
Glycerin ⁵⁹	1% aq 10% aq
Glyceryl monoleate ⁵⁹	30% pet
Hydroxyethyl cellulose ⁵⁹	10% aq
Hydroxypropyl cellulose ³⁵	1% in 30% eth 2% in 30% eth
Isopropyl myristate ^{52,59}	2% pet 5% pet 20% pet 10% eth
Lactose ⁹⁶	As is
Laminated aluminized polyester film	NR
Lanolin ^{59,96}	As is
Menthol ^{52,59}	1% pet 2% pet 5% pet 8% pet
Methacrylates ⁵⁹	2% pet 5% pet
Methyl laurate	NR
Mineral oil ⁵⁹	As is
Pigmented film	NR
Peppermint oil ^{52,59}	2% pet
Plasticizers	NR
Polyolefin	NR
Polyester	NR
Polyethylene glycol (stearate) ⁵⁹	Polyethylene glycol (stearate) ⁵⁸
Polyisobutylene	1% in benzene 2% in benzene
Polypropylene	NR
Polysorbate ⁵⁸	80.5% pet
Polyvinyl alcohol	NR
Povidone ⁵⁹	As is
Propylene glycol ⁵⁹	2% pet
Rubber ⁵⁹	As is
Silicone	NR
Sodium citrate ⁵⁹	1% aq
Sorbitan sesquioleate ^{52,59}	20% pet

aq = aqueous; eth = ethanol; NR = not reported; pet = petrolatum; TTS = transdermal therapeutic system; USP = United States Pharmacopeia.

efficacy and safety of a clonidine TTS. Five (25%) of the patients had positive patch-test reactions to clonidine; 2 of these 5 patients were able to tolerate an oral challenge with clonidine.¹⁹



Figure 3. Positive patch test reaction to the central portion of a reservoir patch.

In 1985, Maibach reported a series of trials performed to determine both the irritation and sensitization potential of clonidine and clonidine TTSs. The irritation study was conducted with two groups of 28 subjects. Group 1 had daily applications of clonidine 3% in petrolatum (pet), petrolatum, a Catapres-TTS (Alza Corp., Palo Alto, CA), and a placebo TTS. Group 2 had daily applications of petrolatum, clonidine 1% pet, clonidine 3% pet, clonidine 9% pet, and clonidine 3% with 0.03% LUE 92 (a contaminant reduction product consisting of two molecules of clonidine and one molecule of acetaldehyde) in petrolatum. The test materials were left in place for 24 hours and were then re-applied daily for 5 days; the last application was left in place over a weekend. The sites were evaluated at each removal, for a total of 21 days. Ten days after the 21-day irritancy study was completed, the patients were patch-tested with the same materials. Patch-test results were uniformly negative: none of the subjects were sensitized to the test materials.²⁰



Figure 4. Positive patch test reaction to the central portion of a reservoir patch. The ingredient common to both reservoir patches in Figure 3 and Figure 4 was hydroxypropyl cellulose.

Subsequently, Maibach performed a second set of experiments. In this second study, group 1 consisted of 103 subjects who received thrice-weekly applications of clonidine 9% pet and plain petrolatum. Group 2 consisted of 92 subjects who received thrice-weekly applications of a clonidine TTS and a placebo TTS. The applied material was left in place for 7 days. Three weeks later, the subjects were challenged with placement of the test materials at a separate site for 72 hours. Weekly applications at the original site were performed for another 2 weeks. The subjects were then rechallenged with the test materials and were evaluated at 24 hours and again at 48 hours after application. At the end of the study, both groups were cross-challenged with the other group's test materials. Group 1 subjects were found to have negative reactions at all evaluations as well as after cross-challenge with the clonidine TTS. In group 2, however, 4 patients (4.3%) demonstrated sensitization to clonidine. The fact that allergic contact dermatitis was observed only in the group tested with the clonidine TTS and not in the group tested with clonidine in petrolatum suggests that some factor in the TTS system enhances sensitization, possibly owing to enhanced penetration.²⁰

Nitroglycerin

The use of nitroglycerin TTSs is a common therapy for angina pectoris. Case reports of sensitization to nitroglycerin itself have rarely been reported in the literature.^{4,21-23} Kounis and colleagues conducted a study of continuous and intermittent use of nitroglycerin TTSs with 320 subjects, using three different commercially available brands to assess cutaneous reactions to nitroglycerin TTSs. System A (Pancoran; Novartis, Metamorphosi, Greece) consisted of glyceryl trinitrate, lactose, colloidal silicon dioxide and silicone medical fluid, ethylene vinyl acetate copolymer membrane, and silicone adhesive. System B (Nitrodisc, GD Searle, Chicago, IL) consisted of glyceryl trinitrate, glycerin, purified water, lactose, polyvinyl alcohol, povidone, sodium citrate, and medical-grade unwoven tape. System C (Nitrodyl, Schering-Plough; Lavipharm, Paiania, Greece) consisted of covering foil and adhesive film, which included a drug reservoir and release control system (individual components of this system were not reported). The nitroglycerin concentrations in these three systems were not reported. Twenty-one (6.5%) of the patients experienced skin reactions; 17 of these patients were classified as having local irritant reactions, 4 patients (1.2%) developed localized and remote skin reactions, and 1 patient developed an anaphylactic reaction. Eleven patients (3.4%) discontinued TTS therapy because of a skin reaction.²⁴ Of the 4 patients with local and remote skin findings, 3 were patch-tested

and had positive reactions to both a nitroglycerin solution (0.2 mg/mL) and a nitroglycerin ointment (concentration not reported). The patient who experienced an anaphylactic reaction was not patch-tested.²⁴

Torres and colleagues reported on a woman with pruritus, burning, erythema, and edema at nitroglycerin TTS application sites. She was patch-tested with a standard series, the nitroglycerin TTS, a placebo TTS, and two concentrations of nitroglycerin (0.2% and 2.0% pet). She had positive reactions to the nitroglycerin TTS and to both concentrations of nitroglycerin. Her therapy was changed to sublingual nitroglycerin and oral isosorbide dinitrate, without difficulty.²⁵

Rosenfeld and White reported a man with cutaneous reactions to a nitroglycerin TTS and a nitroglycerin ointment, both of which were used therapeutically. He was patch-tested with lanolin, petrolatum, a saline placebo, a silicone adhesive, a nitroglycerin ointment (concentration not reported), and a nitroglycerin 0.2 mg/mL solution. He had positive reactions to both the nitroglycerin ointment and the nitroglycerin solution. The patient was successfully transitioned to oral isosorbide dinitrate and sublingual nitroglycerin, without cutaneous sequelae.²⁶

Topaz and Abraham reported on two men who presented with painful erythematous edematous crusting reactions in the region of nitroglycerin TTS application sites. They were patch-tested with lanolin, lactose, nitroglycerin 0.2mg/mL in water (aq), nitroglycerin 0.5mg/mL aq, nitroglycerin ointment (concentration not reported), white petrolatum, a silicone adhesive, and a saline placebo. Both patients had negative reactions to all test sites except those of the nitroglycerin solutions and the nitroglycerin ointment.²⁷

Machet and colleagues reported on a man who presented with a diffuse truncal erythematous pruritic eruption 5 months after placement of a nitroglycerin TTS. After switching brands of TTS, his dermatitis progressed to a generalized eczematous eruption, sparing only the face. Numerous erythematous plaques with vesicles were present at TTS application sites on the patient's back. The patient was patch-tested with a standard series, Nitroderm TTS (Novartis, East Hanover, NJ), Discotrine TTS (3M Sante, Cergy-Pontrose, France), and Lenital nitroglycerin spray (Besins, Montrouge, France) (concentration not reported). Nitroglycerin was the only common component among the three preparations. Relevant positive reactions were limited to the three nitroglycerin-containing preparations, which suggests that the nitroglycerin itself was the responsible allergen.²²

Perez-Calderon and colleagues reported on a man who presented with generalized edema, erythema, vesicles,

and lichenification and excoriations, all sparing only the palms and soles, which developed after the use of a nitroglycerin TTS. Patch testing showed positive reactions to Minitran TTS and Nitroderm TTS as well as to nitroglycerin 0.2 mg/mL aq and nitroglycerin 0.5 mg/mL in ethanol. Patch-test reactions to adhesives were negative. It was postulated that the length of exposure and TTS placement at various sites, as well as the excoriations, accounted for the propagation of dermatitis in this case. The patient was able to transition to oral nitroglycerin, without side effects.²¹

Scopolamine

Used for the prevention of motion sickness, scopolamine can be delivered transdermally through a retroauricular TTS, which is typically worn for 72 hours. Gordon and colleagues described 16 (10%) of 164 naval crew members who presented with cutaneous reactions after using scopolamine TTSs to treat motion sickness. The patients presented with pruritus, erythema, and an edematous, vesicobullous, or eczematous reaction on the retroauricular skin confined to the TTS location. Placement of a TTS behind the contralateral ear produced identical reactions. These 16 men had negative patch-test reactions to the placebo TTS (which contained all ingredients except scopolamine), which suggests that scopolamine was the sensitizer.²⁸

There have also been several case reports of sensitivity to scopolamine. Fisher reported on a woman who had used a scopolamine TTS for 3 weeks to prevent motion sickness and who presented with a pruritic eruption under the TTS. She was patch-test positive to scopolamine 2% pet.²⁹ Van der Willigen and colleagues described a man with a retroauricular skin reaction at the site of a scopolamine TTS application. He had been using scopolamine TTSs for 2 weeks. The patient was patch-tested with a standard series, scopolamine TTS, and scopolamine in concentrations of 0.25%, 0.5%, and 1.0% aq. Patch-test results were positive for the three scopolamine aqueous concentrations and for the scopolamine TTS.³⁰ Similarly, Trozak reported on a patient who presented with an eczematous skin rash and pruritus at the site of the application of a scopolamine TTS, as well as nummular eczematous reactions at previous application sites. Patch-test reactions to scopolamine 1.8% pet were positive; reactions to the other components of the TTS and to tropicamide and atropine were negative. These findings suggest that the tropic acid residue, which is common to all three compounds, was not the antigenic portion of the molecule.³¹ No cross-sensitivity between scopolamine and atropine has been demonstrated although they differ structurally only in an oxygen bridge between atoms 6 and 7 at the organic base of

scopolamine.^{30,32} These findings suggest that the antigenic portion may be the oxygen bridge.³⁰

Testosterone

Testosterone TTSs are used for testosterone-deficient men and improve mood, fatigue, and sexual function.¹² Irritant contact dermatitis is the most commonly reported skin reaction although there have been few case reports of allergic contact dermatitis from the testosterone component of the TTS.³³ Buckley and colleagues reported on a man with Klinefelter's syndrome who presented with erythema and vesiculation at testosterone TTS application sites. He had positive patch-test reactions to testosterone propionate and negative reactions to other components of the TTS (methyl laurate, glyceryl monooleate, carbomer 1342, and polyethylene).³⁴ Shouls and colleagues reported on a man with erythema, blistering, and induration at TTS application sites; this progressed to generalized erythema after 3 months of TTS use. The patient had positive patch-test reactions to testosterone enanthate and testosterone undecanoate.³³

Estradiol

Estradiol TTSs are used to treat menopausal symptoms. There are few case reports of allergy to the estradiol component of the TTS. Boehncke and Gall reported on a woman who had been taking oral estrogen and was switched to estradiol TTS. After the ninth application, she presented with pruritic erythema at the application site; the erythema then spread, resulting in generalized urticarial plaques. Patch testing with the TTS and with individual components of the TTS yielded positive reactions to estradiol-17 β 1%, 2%, and 4% in 96% ethanol, as well as to the complete estradiol TTS. Oral estrogen was reinstated without cutaneous effects.³⁵ Carmichael and Foulds reported on a woman with contact allergy to an Estraderm TTS (Novartis Pharmaceuticals). She was tested with the complete Estraderm TTS and to a placebo TTS that contained all ingredients except estradiol-17 β . She reacted only to the Estraderm TTS, which suggests that estradiol-17 β was the allergen.³⁶

Koch described a woman who presented with a pruritic, discoid, indurated, erythematous plaque at the site of an estradiol TTS application. This was followed by a bullous reaction. She was transitioned to an estradiol-containing gel, but subsequent eczematous reactions also occurred at the site of gel application. Patch testing was performed with a standard series and with the individual components of the TTS and gel. Positive reactions to estradiol 1% and to

norethisterone acetate 1% in ethanol were found. Patch-test reactions to the other components of the TTS (carbopol, triethanolamine, and ethanol) and with the placebo TTS were negative.³⁷ Panhans-Gross and colleagues reported on a woman who presented with a history of cutaneous reactions to many different brands of estradiol TTS.³⁸ Patch-test results were positive for all three estradiol TTSs she had tried, as well as to estradiol 1%, 2%, and 4% in 96% ethanol. Patch-test results for other components of the system including 96% ethanol were negative.

Lamb and Wilkinson reported on a 61-year-old woman with persistent hand and foot dermatitis who developed multiple contact allergies to topical steroids. She had a history of eczematous reactions to estradiol-17 β and to norethisterone-containing TTSs. Patch testing was performed with a standard series, a shoe series, a corticosteroid series, and a sex steroid series. The patient had positive reactions to hydroxyprogesterone, progesterone, estradiol, betamethasone valerate, and clobetasol propionate, as well as numerous other steroids. This case demonstrated a potential cross-reaction between topical corticosteroids and sex steroids, and patients who develop contact allergies to sex steroids may be at risk of developing corticosteroid allergies.³⁹

Nicotine

Nicotine TTSs are used as aids in smoking cessation. Nicotine is not particularly antigenic, and nicotine allergy in smokers and tobacco workers is rare. However, allergic contact dermatitis from nicotine has been reported among nicotine TTS users. It is hypothesized that cutaneous exposure to nicotine allows the molecule to penetrate the epidermis, and binding of this hapten with skin proteins may form a neoantigen, which may induce sensitization.⁴⁰ Jordan reported on a two-phase trial involving 186 subjects. Phase one was an open-label study and involved only active nicotine TTSs. Phase two was a 4-day randomized double-blind challenge. Three (1.6%) of the patients were sensitized as determined by positive reactions to rechallenge.⁴¹

Several other studies have reported cutaneous reactions to nicotine. In a double-blind study involving 183 smokers, 29 (15.8%) complained of pruritus and 18 (10%) reported erythema. Of 7 patients who had a papulovesicular rash, 6 were patch-tested with a nicotine TTS, a placebo TTS (without nicotine), matrix material, gauze, and a standard series (lacquer, adhesives, and plastics); 5 of these patients had positive patch-test reactions to nicotine. Six patients (3.3%) dropped out of the study because of cutaneous reactions.⁴² Similarly, Vincenzi and colleagues reported on five patients with cutaneous reactions at nicotine TTS ap-

plication sites. Six patients were patch-tested with a standard series, nicotine 1% and 10% aq, and carrageen (a thickening, stabilizing, or emulsifying agent used in pharmaceutical, industrial, and food products) as is and had positive reactions to nicotine 10% aq; one patient also had a positive reaction to nicotine 1% aq.⁴³ Färm reported a woman with diffuse eczema at past nicotine TTS application sites and a papulovesicular rash in other areas. The patient was patch-tested with a nicotine TTS, a placebo TTS, and nicotine base in six different aqueous concentrations (0.1%, 0.3%, 1%, 3%, 10%, and 30%); she had positive patch-test reactions to nicotine in 3%, 10%, and 30% aqueous concentrations.⁴⁴

Fentanyl

Fentanyl is a potent opioid analgesic used to treat pain. Cutaneous reactions (involving papules, pustules, erythema, and pruritus) to fentanyl TTSs have been described.^{45–49} There were two reports of diffuse cutaneous reactions thought to be due to fentanyl TTS, but patch testing was not performed on either of these patients.^{50,51}

Other TTS Ingredients That Can Cause Allergic Contact Dermatitis

Contact dermatitis is associated not only with the active ingredients of transdermal systems but also with other components. Various adhesives and other components of the TTS reservoir, such as alcohol and anesthetics, have been shown to cause allergic contact dermatitis.¹⁷

Peppermint and Menthol

Foti and colleagues described a man with eczematous contact dermatitis in the lumbar region where he had applied a flurbiprofen LAT patch for relief of back pain. Peppermint and menthol were added to the LAT patch for their anesthetic properties and to aid vasodilation and drug penetration. The patient was patch-tested with the LAT patch in toto, as well as with its components (flurbiprofen 2% pet, isopropyl myristate 5% pet, polysorbate 80.5% pet, sorbitan sesquioleate 20% pet, peppermint oil 2% pet, and menthol 1% pet). The patient had positive reactions to the patch in toto and to menthol and peppermint and a weak reaction to fragrance mix. Menthol is a rare sensitizer but has been shown to undergo metabolism to menthone, which may induce sensitization.⁵²

Hydroxypropyl Cellulose

Schwartz and Clendenning described a woman with pruritus, erythema, edema, and postinflammatory hyper-

pigmentation at sites where an estradiol TTS containing hydroxypropyl cellulose, estradiol, and alcohol had been applied. Patch tests with components of the system yielded 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. Because the patient had a negative result for hydroxypropyl cellulose in water, it was thought that the vehicle was important for allergen penetration and potential sensitization.⁵³

Polyisobutylene

Groth and colleagues observed 29 patients who were using clonidine TTSs. Patch testing was performed on 7 patients; 1 patient had a positive reaction to polyisobutylene.¹⁸

Ethanol

Irritation due to ethanol is common, but ethanol allergy is rare and can be missed.⁵⁴ Patients who are topically sensitized to ethanol may develop local and generalized dermatitis from the consumption of alcoholic beverages.^{55,56} Cross-reactions with other aliphatic alcohols and acetone have been reported.⁵⁴ Pecquet and colleagues reported on two patients who were using estradiol TTSs to treat disabling menstrual headaches and who presented with pruritic erythematous lesions at TTS application sites. Both patients were patch-tested, and positive results were obtained for ethanol, TTS with ethanol and no estradiol, TTS with ethanol and estradiol, and hydroxypropyl cellulose in ethanol (concentrations not reported). Occlusion may have promoted the sensitization.⁵⁷

Grebe and colleagues described a woman with erythema, induration, vesicles, itching, and burning at estradiol TTS application sites. The patient was not patch-tested, and she was transitioned to oral ethinylestradiol. Her rash progressed within 48 hours, and she experienced systemic symptoms (including facial edema, reddening, generalized pruritus, and a fine macular rash on her face and upper trunk) along with re-activation of the dermatitis at TTS application sites. Oral ethinylestradiol therapy was discontinued, and her reaction subsided within 48 hours. She was patch-tested with six items: a TTS without estradiol, a TTS without estradiol and ethanol, a TTS without a drug reservoir and with occlusive adhesive (3M, St. Paul, MN), a TTS without a drug reservoir and with non-occlusive adhesive (3M), a TTS without a drug reservoir and with non-occlusive adhesive (polyisobutylene), and a complete estradiol TTS. Patch-test reactions to the TTS without estradiol and to the complete estradiol TTS were

positive, suggesting an allergy to ethanol. Further patch testing with 0.1 mL each of pure ethanol, pure isopropyl alcohol, pure N-propyl alcohol, and fluid aspirated from the estradiol TTS reservoir showed positive reactions to ethanol and the fluid from the estradiol TTS. The patient recalled drinking two alcoholic beverages the night before the onset of the systemic symptoms. Previously, she had no adverse reactions to alcoholic beverages. Rechallenge with oral ethanol again produced a systemic reaction, and oral ethinylestradiol was restarted, without side effects.⁵⁸ Although patch testing with 100% alcohol has been reported, repeated testing with lower concentrations (such as 10%) is recommended.⁵⁹

Adhesives

Adhesives are necessary for adherence of a TTS to the skin. Several publications have implicated adhesives as allergens. McBurney and colleagues reported on 9 women who had discontinued their use of estradiol TTSs because of skin reactions and who were subsequently patch-tested; 4 patients had positive patch-test reactions to the adhesive, and 2 of these 4 patients also had positive reactions to the placebo TTS. The allergen common to these two systems was the adhesive.⁶⁰ Fisher described a man who developed a pruritic eruption at the site of a nitroglycerin TTS; a similar reaction occurred at a second site upon application. Patch testing was performed with adhesive materials, foil backing, a nitroglycerin TTS, and a placebo TTS. The patient showed positive patch-test reactions to only the adhesive material.²⁹ Kounis and colleagues performed a study of continuous and intermittent use of nitroglycerin TTSs on 320 patients, using three different commercially available brands to assess cutaneous reactions to nitroglycerin TTSs. Thirteen (4%) of the 320 patients had positive patch-test reactions to a silicone adhesive (specific name and concentration not reported).²⁴

Dwyer and Forsyth described a man who presented with inflammation and irritation at nicotine TTS application sites. The manufacturer of the TTS reported its ingredients to be the following: (1) nicotine; (2) copolymer of 2-ethylhexyl acrylate, hydroxyethyl acrylate, glycidyl methacrylate, and vinyl acetate; (3) copolymer of ethyl acrylate and methyl methacrylate; and (4) a neutral oil containing a mixture of triglycerides of saturated vegetable fatty acids. Patch tests were performed with a standard series, the inner and outer layers of the nicotine TTS, two preparations of nicotine (5% aq and 5% in ethanol), a plastics and glues series, and an antimicrobial series. Positive reactions were observed to both layers of the nicotine TTS, triethylene

glycol dimethacrylate, ethylene glycol dimethacrylate, 1,4-butanediol dimethacrylate, 2-hydroxyethyl methacrylate, m-m-dimethylaminoethyl methacrylate, tetrahydrofurfuryl-2-methacrylate, and p-phenylenediamine.⁶¹

Other Components

Several investigators reported eliminating the active drug as the culprit but were unable to identify the offending allergen.^{25,42,60,62} Another ingredient implicated in allergic contact dermatitis from TTSs is glycerin.²⁴

Neoantigens

Di Landro and colleagues reported allergic contact dermatitis from a Nitroderm TTS in a patient who presented with erythematous vesicular lesions over the entire body but sparing the head and distal portions of the extremities. He was subsequently patch-tested with nitroglycerin at concentrations of 0.5%, 1%, 2%, and 3% in petrolatum and with a placebo TTS; the results were negative. His only positive reaction was to the complete Nitroderm TTS. The authors did not test individual components of the TTS, other than the nitroglycerin, but hypothesized that because no reaction was observed to the placebo TTS (which contained all the other ingredients except nitroglycerin), it may have been a neoantigen or the complex of chemicals in the TTS that provoked sensitization.⁶³

Corazza and colleagues described a woman who presented with erythematous vesiculation and pruritus at the site of application of a clonidine TTS. She was patch-tested with clonidine as well as the other individual components of the transdermal system and the entire system itself. She had a positive patch-test reaction only to the complete clonidine TTS system.¹⁷ During manufacture, clonidine and acetaldehyde can form a reactive condensation product (called LUE) that consists of two molecules of clonidine and one molecule of acetaldehyde.²⁰ This neoantigen may have been the sensitizing agent in this case.^{17,64}

Systemic Tolerance

Most patients are able to successfully transition to oral medication after failing transdermal therapy because of allergic contact dermatitis.^{4,19,21,25,26,64,66,67,95} For the 31 patients patch-test-positive to clonidine who were orally challenged, 30 had no cutaneous or systemic effects.^{19,95} One patient had a skin reaction consisting of localized erythema and edema at a previous clonidine TTS site after taking oral clonidine. None of the rechallenged patients experienced a systemic reaction.⁹⁵ Nitroglycerin was toler-

ated by 4 out of 4 patch-test-positive patients who underwent oral challenge.^{4,25,26,64} Nicotine caused no systemic or skin symptoms in 7 out of 7 patients who patch-tested positive for nicotine allergy and later resumed smoking.⁶⁶ However, most drug manufacturers do not recommend oral challenge for patients topically sensitized to drugs.

A literature search found no reports of patients with contact allergy to nicotine who experienced a relapse of dermatitis or systemic skin reactions after stopping the TTS and restarting smoking.⁶⁶ However, a case report discussed earlier in this paper reported a woman who began chewing nicotine-replacement gum after discontinuing nicotine TTS due to widespread cutaneous reaction, and positive patch testing to nicotine. Her cutaneous symptoms progressed despite treatment with topical corticosteroids. Her widespread dermatitis was possibly worsened by her continued nicotine intake. There were no local reactions in her mouth, however, and the patient continued to smoke after stopping the gum. Her skin lesions cleared two weeks after cessation of the nicotine gum, and the dermatitis did not return.⁴⁴

Decreased Absorption of Active Medication at the TTS Site

Dermatitis at the site of a TTS can cause decreased absorption of active medication. Carmichael and Foulds described a man who had irritation, redness, and induration at nitroglycerin TTS application sites. In addition, the patient experienced a worsening of his angina, which was postulated to be because of decreased drug delivery via the irritated skin.⁴ Similarly, White and Guidry described a woman who presented in the eleventh week of transdermal clonidine treatment with hypertension, nausea, light-headedness, and headache in conjunction with painful pruritus, edema, erythema, and vesiculation at the TTS site. Her symptoms were thought to be consistent with contact dermatitis and clonidine withdrawal syndrome. The authors proposed that the clonidine was not being absorbed, owing to cutaneous inflammation caused by the contact dermatitis reaction.⁶⁸

Type I Immunoglobulin-Mediated Reactions

Nicotine and nitroglycerin TTSs have been reported to cause immediate reactions.^{24,40,43} Kounis and colleagues described a patient who developed an anaphylactic reaction after application of a glyceryl trinitrate TTS. The patient developed a painful generalized erythematous pruritic eruption. Mucous membranes and eyes were swollen,

in addition to the formation of two wheals on the forehead and right side of the face. Patch testing was not performed, and the symptoms resolved upon treatment with steroids and antihistamines.²⁴

Rilliet and colleagues described a woman who presented with an urticarial rash on her ears and with reported erythema after applying perfume, disinfecting her hands with alcohol, and drinking alcoholic beverages. Patch testing with ethanol, propyl alcohol, butyl alcohol, and amyl alcohol produced urticaria.⁶⁹ This case was not associated with the use of a TTS, but because ethanol is a common component of TTSs, it is possible that contact urticaria could result from a TTS containing ethanol.

Management of Cutaneous Reactions to TTS

Management of cutaneous reactions includes rotation of application sites, TTS placement on the buttocks, trials of alternate brands, a shorter duration of occlusion, and pretreatment of the skin with topical corticosteroids.^{1,24,70-74} Davis and Winter evaluated 3,816 TTS sites on 53 women who were using Estraderm 0.05 placebo TTSs and who were tested against a control adhesive TTS. The authors found that irritant reactions were minimized (92% decrease in cumulative irritation score) by rotation of application sites and placement on the buttocks rather than the abdomen or lower back.⁷¹ Kounis and colleagues reported that 10 of 21 (48%) patients who experienced cutaneous reactions to one brand of nitroglycerin TTS were able to successfully transition to another brand, with no cutaneous side effects, indicating that a change of brand in some cases might help avoid future reactions.²⁴ For 3 months, Weber and Drayer observed 101 patients using clonidine TTS and suggested that cutaneous reactions might be improved by decreasing the occlusion time from 7 days to 3 to 5 days.⁷⁰

Pretreatment and coadministration of topical steroids with TTSs have been advocated as methods to improve irritation and allergic contact dermatitis at TTS application sites.^{72,75,76} Pretreatment of TTS sites with topical corticosteroids was evaluated in an open-label controlled pilot study of 65 men who each served as his own control. Pretreatment of testosterone TTS placement sites with triamcinolone acetonide 0.1% cream was found to lower the incidence and severity of skin irritation.⁷⁷ Pretreatment of application sites with an aerosol spray containing beclomethasone dipropionate has also been shown to decrease skin reactions among users of clonidine TTSs.¹ In one report, pretreatment of testosterone TTS application sites with clobetasone butyrate 0.05% cream 30 minutes prior to placement was found to prevent dermatitis, without im-

pairment of drug delivery.³³ This regimen enhanced compliance and may work for other patients who have allergic contact dermatitis and who are not candidates for other modes of drug delivery.

Summary

Transdermal therapeutic systems (TTSs) are an increasingly common mode of drug delivery. However, they are ideally suited to produce sensitization because they simulate Kligman's maximization procedure with long-term occlusion and concomitant irritation. Allergy to the active pharmaceutical agents, adhesives, and other components has been described. Irritant reactions are also common but may be managed by rotation of TTS sites and pretreatment with topical corticosteroids. If discontinuation of a TTS is necessary, most patients will be able to successfully transition to the use of oral agents. More research is needed for the development of TTSs that are nonirritating and less sensitizing.

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