

Cutaneous Reactions to Transdermal Therapeutic Systems

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Transdermal therapeutic systems (TTSs) are commonly used to treat many diverse medical conditions. There are several advantages to this form of drug delivery; however, adverse cutaneous reactions are common. This review article provides an update on skin reactions due to TTSs containing medications newly available in TTS form, including buprenorphine, diclofenac, lidocaine, oxybutynin, rotigotine, methylphenidate, rivastigmine, teriparatide, and nicardipine.

TRANSDERMAL DRUG DELIVERY SYSTEMS are increasingly prescribed instead of oral formulations because of several potential advantages, including convenience and increased patient compliance. Another benefit is the avoidance of first-pass metabolism and fluctuating plasma concentrations. Most patients experience fewer side effects with transdermal drug delivery systems than with oral delivery of drugs; however, skin reactions can have a negative impact on compliance. Although skin reactions are common, it is possible to minimize their incidence and to manage their signs and symptoms.¹

Nineteen drugs are currently available in transdermal therapeutic systems (TTSs) in the United States, including lidocaine, nitroglycerin, nicardipine, nicotine, scopolamine, estradiol, testosterone, clonidine, oxybutynin, ketoprofen, diclofenac, fentanyl, and buprenorphine.^{2,3} Several others are in clinical trials.

Our group published a comprehensive review of skin reactions to TTSs in 2006, covering reactions to TTSs containing nitroglycerin, nicotine, scopolamine, estradiol, testosterone, clonidine, and fentanyl.¹ The purpose of this review is to provide an update on reactions associated with medications that are newly available in TTS form, including buprenorphine, diclofenac, lidocaine, oxybutynin, rotigotine, methylphenidate, rivastigmine, teriparatide, and nicardipine.

TTS Types

A TTS has three components: (1) an active pharmaceutical drug, (2) an adhesive, and (3) enhancing agents. Several types of TTS are currently available, including matrix,

local-action transcutaneous, and reservoir TTSs. The matrix TTS is the most common type and contains a single-layer mixture of adhesive, active ingredient, and other components that directly contact the skin. A local-action transcutaneous TTS is used to deliver nonsteroidal antiinflammatory drugs (NSAIDs) through the skin; it is similar to the matrix TTS, except a nonwoven polyester backing supports the nonsteroidal antiinflammatory drug formulation. A reservoir TTS is composed of a depot of liquid containing the active ingredient, which is released through a rate-controlling membrane.¹ Newer methods of drug delivery through the skin include programmable battery-powered carbon nanotube membrane TTSs and transdermal microneedle TTSs.^{3,4}

Irritant Contact Dermatitis and TTSs

Irritant contact dermatitis (ICD) is the most common type of application-site reaction and usually consists of erythema with itching or burning. These reactions are usually transient (most often characterized as mild to moderate in severity) and occur in 20 to 50% of patients.⁵ Most irritant reactions are localized to the site of application and resolve spontaneously within several days of TTS removal. These skin reactions usually cause minimal discomfort to the patient and are unlikely to be of medical consequence. Most patients continue to use the TTS despite skin problems.^{5,6} Recommendations for the treatment and prevention of ICD are listed in Table 1.^{5,7}

Allergic Contact Dermatitis and TTSs

Allergic contact dermatitis (ACD) from a TTS is relatively rare. ACD is a type IV cell-mediated hypersensitivity reaction that presents with bright red erythema, indurated papules, vesicles, and intense itching. Allergens include the

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Table 1. Recommendations for Treatment and Prevention of Irritant Contact Dermatitis*Prevention*

- Rotation of TTS application site
- Careful removal of TTS

Treatment

- Gentle skin care
- Use of moisturizers
- Topical corticosteroids if necessary

Adapted from Ale I et al.⁵; Warshaw EM et al.⁷

TTS = transdermal therapeutic system.

active ingredient, adhesive, or inactive ingredients. ACD is diagnosed by patch testing. Recommended patch-test concentrations for the active ingredients reviewed in this article are listed in Table 2. Table 3 lists the distinguishing features of ICD and ACD.

Most individuals who are sensitized to the active ingredient in a TTS can tolerate the same drug in oral form. However, drug manufacturers generally do not recommend oral rechallenge once a patient has been sensitized.^{1,6,8,9}

All components of TTSs have the potential to cause ACD or ICD.¹ Ingredients of newly approved TTSs are listed in Table 4.^{10–14}

“Newer” TTSs***Buprenorphine***

Buprenorphine has been available in Europe since 2001 in a TTS in three dosages (35.0 µg/h, 52.5 µg/h, and 70.0 µg/h). A buprenorphine TTS was approved for use in the United States in 2010. This opioid analgesic is of a low molecular weight and is lipophilic, characteristics that are ideal for delivery through a TTS.^{2,15,16} Local adverse reactions (mainly erythema and pruritus) are common; it

has been reported that 35.6% of patients experience some type of mild-to-moderate skin reaction upon the removal of the TTS.²

Schmid-Grendelmeier and colleagues (in a study sponsored by Janssen-Cilag, Baar, Switzerland) compared buprenorphine and fentanyl TTSs in 46 healthy volunteers. They found that irritant skin reactions were more common with the buprenorphine TTS than with the fentanyl TTS. The investigators assessed the presence of erythema and reaction severity after the removal of a single application of both a fentanyl 25 µg/h TTS (Duragesic, Janssen-Cilag) and a buprenorphine 35 µg/h TTS (Transtec, Napp Pharmaceuticals, Cambridge, UK). Sixty minutes after removal, there was a trend toward a higher incidence of erythema with the buprenorphine TTS as compared to the fentanyl TTS, whereas the severity of erythema as measured by chromometric assessment was significantly greater in the buprenorphine group ($p = .01$). The incidence of erythema 72 hours after removal was also higher with buprenorphine (22% vs 5%, $p = .04$). Topical adverse events were less frequent with fentanyl (one event with fentanyl vs six events with buprenorphine).¹⁷

ICD is much more common than ACD among users of the buprenorphine TTS. During the clinical development of the buprenorphine TTS, three double-blind placebo-controlled parallel group studies and one open-label follow-up study were conducted; in these, 25% of patients reported erythema and 22% reported pruritus. All these events were considered mild or moderate.¹⁸

In a postmarketing surveillance study, 109 (0.8%) of the 13,179 patients surveyed reported contact dermatitis (allergic vs irritant not specified). Patch testing, if performed, was not reported. In addition, 0.7% reported pruritus, and 0.5% reported an erythematous rash.¹⁹

Several patients with ACD from a buprenorphine TTS have also been reported. Callejo Melgosa and colleagues reported the case of a 70-year-old woman with itching localized to the application site of a buprenorphine 35 µg/h

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

<i>TTS Component</i>	<i>Reported Patch-Test Concentrations</i>	<i>References</i>
Buprenorphine	Buprenorphine 0.005% and 1% aq, 0.001% and 0.002% pet Buprenorphine TTS as is Injectable buprenorphine (0.3% aq) as is	2, 15, 16
Diclofenac	Diclofenac 0.1% as is, 1% pet, 2% pet, 2.5% pet Diclofenac sodium 10% pet Diclofenac diethylamine 10% pet	24, 25, 26, 27
Methylphenidate	10% and 0.1% pet, 10% and 0.1% aq	43

aq = aqueous; pet = in petrolatum; TTS = transdermal therapeutic system.

Table 3. Comparison of Allergic and Irritant Contact Dermatitis

<i>Frequency</i>	<i>Allergic Contact Dermatitis</i>	<i>Irritant Contact Dermatitis</i>
	<i>Uncommon</i>	<i>Common</i>
Pathophysiology	Type IV cell-mediated hypersensitivity reaction	Nonspecific nonimmune mediated response to irritation
Clinical characteristics	Usually bright erythema, indurated papules and plaques; may have vesicles; intense pruritus	Nonspecific skin reaction including erythema and mild-to-moderate pruritus
Localization	May spread beyond initial application site	Localized to application site

TTS (Transtec). Symptoms started 10 hours after application of the TTS and resolved after 15 days of treatment with a topical corticosteroid. Patch testing was performed with Transtec “as is” and with the “ingredients” as well as with both 0.005% and 1% aqueous (aq) concentrations of purified buprenorphine. Patch-test readings at 48 and 96 hours were positive (erythema, infiltration, and blisters) for the Transtec TTS “as is” and for both concentrations of purified buprenorphine. All other ingredients yielded negative results.¹⁵

In another case, an 81-year-old woman presented for evaluation of itching and redness on her back after having used a buprenorphine TTS (Transtec) for 2 weeks. Five well-delineated red plaques corresponding to the sites of TTS application were present. The authors observed desquamation, vesiculation, and yellow crusts, which extended beyond the red plaques. Patch testing was performed with Transtec 35 µg/h (“as is” and with adhesive only), buprenorphine 0.3 mg injectable solution “as is,” and purified buprenorphine 0.001% and 0.002% in petrolatum (pet). All four test sites containing buprenorphine were strongly positive on days 2 and 4, whereas the Transtec adhesive-only test caused no reaction. The patient was switched to a fentanyl TTS, with no adverse effects.²

Vander Hulst and colleagues described five patients ranging in age from 63 to 90 years who had all developed persistent pruritic erythematous plaques at buprenorphine TTS application sites. Two of the five additionally had a generalized eczematous skin eruption, and one also experienced episodes of bronchospasm. All five were patch-tested with the Transtec TTS “as is”; four were also patch-tested with a placebo TTS. One patient was tested with three other formulations of buprenorphine: intravenous buprenorphine solution 0.3% aq and sublingual buprenorphine (0.2 mg tablet) in powder form (both “as is” and moistened with water). All five patients were found to have patch test–proven ACD from buprenorphine. The two patients with generalized eczematous rashes and

bronchospasm found that these symptoms improved after discontinuation of the buprenorphine TTS. The authors also performed patch tests with buprenorphine TTS in 28 healthy controls, all of whom had negative reactions.¹⁶

None of the reactions to buprenorphine TTSs have clearly involved anaphylaxis. However, one of the patients described did report airway symptoms associated with the use of the patch. It is worth noting that sublingual buprenorphine was used successfully in the desensitization of an opiate-dependent patient with immunoglobulin E (IgE)–mediated anaphylaxis to buprenorphine.²⁰

Diclofenac

The diclofenac epolamine TTS (1.3%) has been in use in Europe since 1993 and was approved by the US Food and Drug Administration in 2007 for treatment of pain due to minor sprains, strains, and contusions. It was the first topical NSAID patch to be approved in the United States.²¹

In a 2010 double-blind placebo-controlled trial conducted by Hsieh and colleagues, 153 patients were randomized to either a diclofenac (60 mg) TTS or a control TTS (containing menthol) for myofascial pain. The TTSs were applied three times daily for 7 days. The skin was evaluated at baseline and at 4 and 8 days after application. The most frequently observed adverse effect in both groups was skin irritation (described as dry skin, erythema, papules, itching, or a cooling sensation), which was significantly more frequent in the control group than in the treatment group (16–18% vs 3–6%, $p < .05$). All adverse effects spontaneously resolved by the end of the study, with no additional treatment.²² The increased irritation in the control group may have been attributable to menthol because menthol was not an ingredient of the active TTS.

In clinical trials of 1,599 diclofenac TTS and 968 placebo TTS patients, no differences in adverse events were observed; the most common events (4%) were mild skin erythema and pruritus.²³ Between June 1993 and July

Table 4. Ingredients in Newly Approved Transdermal Therapeutic Systems

<i>Brand Name</i>	<i>Manufacturer</i>	<i>Active Ingredient</i>	<i>Backing Layer</i>	<i>Release Liner*</i>	<i>Drug/Adhesive Matrix</i>	<i>Other Adhesive</i>	<i>Listed Inactive Ingredients</i>
Duragesic ¹⁰	Ortho-McNeil-Janssen (Raritan, NJ)	Fentanyl	Polyester/ethyl vinyl acetate film	Ingredients not listed separately	Drug in adhesive layer	Not listed	Remaining components listed only as "pharmacologically inactive"
Transtec ^{11†}	Napp (Cambridge, UK)	Buprenorphine	Polyethylene terephthalate	Polyethylene terephthalate foil, siliconized and coated on one side with aluminum	[(Z)-Octadec-9-en-1-yl] oleate, povidone, 4-oxopentanoic acid, poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinyl acetate], cross-linked	Poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinyl acetate], not cross-linked	Not listed
Butrans ¹⁰	Purdue Pharma (Stamord, CT)	Buprenorphine	Beige-colored web backing (ingredients not listed separately)	Not listed	Buprenorphine-containing adhesive matrix	Adhesive rim without buprenorphine	Levulinic acid, oleyl oleate, povidone, polyacrylate cross-linked with aluminum
Flector ¹⁰	King (Bristol, TN)	Diclofenac epolamine	Nonwoven polyester felt	Polypropylene	Drug in adhesive layer	Not listed	1,3-Butylene glycol, dihydroxyaluminum aminoacetate, disodium edetate, D-sorbitol, fragrance (Dalin PH), gelatin, kaolin, methylparaben polysorbate 80, povidone, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, tartaric acid, titanium dioxide, purified water

Table 4. Continued

Brand Name	Manufacturer	Active Ingredient	Backing Layer	Release Liner*	Drug/Adhesive Matrix	Other Adhesive	Listed Inactive Ingredients
Lidoderm ¹⁰	Endo (Chadds Ford, PA)	Lidocaine	Nonwoven polyester felt	Polyethylene terephthalate film	Lidocaine and adhesive mixture	Not listed	Dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, poly-acrylic acid, poly-vinyl alcohol, propy-lene glycol, propyl-paraben, sodium carboxy-methylcellulose, sodium polyacrylate, D-sorbitol, tartaric acid, urea
Oxytrol ¹²	Watson Pharma (Morristown, NJ)	Oxybutynin	Flexible polyester/ethylene vinyl acetate film	Siliconized polyester strips	Cast film of acrylic adhesive with oxybutynin and triacetin	Not listed	Not listed
Neupro ^{13‡}	Schwarz Pharma (Milwaukee, WI)	Rotigotine	Polyester film siliconized, and aluminized, and color-coated with a pigment layer (titanium dioxide, pigment yellow 95, pigment red 166) and imprinted (pigment red 144, pigment yellow 95, pigment black 7)	Fluoropolymer-coated polyester film	Drug/adhesive layer with poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate (silicone adhesive), ascorbyl palmitate, povidone, sodium metabisulfite, dl- α -tocopherol	Not listed	Not listed
Daytrana ¹⁴	Noven (Miami, FL)	Methylphenidate	Polyester/ethylene vinyl acetate	Fluoropolymer-coated polyester	Acrylic adhesive, silicone adhesive, methylphenidate	Not listed	Listed only as "pharmacologically inactive"
Exelon ¹⁰	Novartis (East Hanover, NJ)	Rivastigmine	Flexible polymer	Ingredients not listed separately	Drug in acrylic matrix	Silicone adhesive matrix	Acrylic copolymer, poly(butylmethacrylate, methylmethacrylate), silicone oil, vitamin E

*Removed prior to application.

†Not available in the United States.

‡Withdrawn from US market; still available in Europe.

2007, 99 adverse events (AEs) were spontaneously reported to the marketing authorization holder; this corresponds to a rate of 10 per million 1-week treatment courses. These AEs included (but were not limited to) skin reactions such as erythema, pruritus, blistering, and dermatitis. No patch testing was reported. Stevens-Johnson and related syndromes were not reported.²³

Although there are no documented cases of ACD from diclofenac TTSs, there are at least four reported cases of contact allergy due to the active ingredient in diclofenac gel (Solaraze, Pharmaderm, Melville, NY).^{24–26} One patient showed positive patch-test reactions to diclofenac sodium 10% pet and diclofenac diethylamine 10% pet on day 4.²⁴ Two patients were patch test positive to diclofenac 2.5% pet,²⁵ and one patient was patch test positive to diclofenac 0.1% “as is” and diclofenac 2% pet.²⁶ Another patient experienced an anaphylactic reaction during patch testing with diclofenac. The patient previously had an anaphylactic reaction 5 minutes after the use of a 100 mg diclofenac sodium suppository and had a history of respiratory problems after the ingestion of diclofenac. She was patch-tested on the right arm with diclofenac 1% pet. Fifteen minutes after the diclofenac patch was placed, she developed dyspnea, hoarseness, and headache. The patch was removed immediately, and the patient was treated with inhaled salmeterol and with 2 mg of clemastine intramuscularly. She did not develop a wheal at the site of the diclofenac patch. The report’s authors advocated a period of observation after the placement of patch tests containing NSAIDs in patients with a history of anaphylactic reactions to NSAIDs.²⁷

Lidocaine

The lidocaine TTS consists of 5% lidocaine (700 mg) in a large (10 × 14 mm) stretchy adhesive patch.²⁸ In clinical trials, the most common AE reported was skin rash or redness at the application site (28%); however, this reaction was also experienced by a similar percentage of patients treated with a vehicle TTS alone (34%).²⁹

A telephone study of 20 patients successfully treated with a 5% lidocaine medicated plaster for localized neuropathic pain was undertaken to assess the efficacy and tolerability of the lidocaine 5% TTS. Patients were contacted for a telephone interview after 3 and 5 years of therapy. Patients were questioned in regard to the efficacy, tolerability, wear time, and comfort of the TTS and the development of tolerance to it. Two patients experienced reversible erythema (without edema or blistering) localized to the application site when the TTS was left in place for longer than the recommended

12 hours (16 hours in this case). This was the only side effect reported. After decreasing the time to 10 hours, the local reactions significantly improved with continued TTS use.³⁰

Argoff and colleagues conducted an open-label nonrandomized prospective 2-week study involving 77 patients to determine the impact of the lidocaine 5% TTS on painful diabetic neuropathy, lower back pain, and pain associated with postherpetic neuralgia. The TTS was applied to the area of maximal pain, with no more than four patches changed every 24 hours. Safety was assessed by AEs, dermal assessment of application sites, and skin sensory testing. Overall, eight patients (10%) experienced mild-to-moderate treatment-related AEs but no serious AEs. No patient discontinued treatment because of skin side effects. Although local side effects (including erythema) occurred, they were relatively mild and resolved spontaneously. (Data on skin side effects were not reported separately.) The side effects occurred both with the lidocaine 5% TTS and with the placebo TTS, suggesting causes other than the active ingredient.³¹

A recent pharmacokinetic study of the lidocaine 5% TTS also assessed its safety and tolerability over an extended period in healthy adults. This open-label multi-dose study involved the application of four lidocaine TTSs to the upper back for 18 hours (with a 6-hour rest period) over 3 consecutive days. Erythema and edema (grades 0–4) were assessed at the application sites. Eighteen subjects reported very slight-to-moderate (grade ≤ 2) erythema. No patients reported grade 3 or grade 4 erythema; one subject reported grade 1 edema.³² No patch testing was reported.

Over the 14-day treatment period in a double-blind crossover trial of 32 patients, skin redness or rash was reported by 9 patients with lidocaine patches and 11 patients with vehicle patches.³³ In another double-blind crossover trial, involving 35 patients, skin reddening at the application site was reported by two patients (one with a lidocaine patch and one with a vehicle patch).³⁴

Although type I IgE-mediated immediate-type allergic reactions to parenteral amide anesthetics such as lidocaine are considered less likely than such reactions to ester anesthetics, the likelihood of ACD from topical anesthetics is less clear-cut than type I reactions from injectable anesthetics.³⁵ In a retrospective cross-sectional analysis of data from more than 10,000 patients patch-tested with topical anesthetics, no consistent cross-reaction patterns were found within amide or ester groups. Only 66 patients (0.7%) were patch test positive to lidocaine.³⁶

Oxybutynin

Anticholinergic medications such as oxybutynin are currently considered the standard of care for patients with overactive-bladder conditions. Oxybutynin is a lipophilic drug formulated in a matrix-type TTS.^{37–39}

A randomized open-label community-based study of 2,878 adults with overactive bladder was conducted to assess health-related quality of life and safety with a 3.9 mg/d oxybutynin TTS (Oxytrol, Watson Pharma, Corona, CA) applied for no more than 6 months. Fourteen percent of the patients experienced drug-related application-site reactions, including pruritus, erythema, dermatitis, and irritation. No patch testing was reported.⁴⁰ A 12-week double-blind double-dummy study compared the safety and efficacy of a 3.9 mg/d oxybutynin TTS and oral long-acting tolterodine with placebo in 361 adults. The oxybutynin TTS was applied twice weekly. The most common AEs were localized application-site pruritus (14.0% vs 4.3% with placebo) and erythema (8.3% vs 1.7% with placebo). Twenty-six of the 32 skin AEs were judged by patients to be mild or moderate. Twelve patients in the oxybutynin TTS group discontinued treatment because of skin reactions. No patch testing was reported.³⁸

In another multicenter double-blind study, 520 patients were randomized to receive three applications of oxybutynin TTS (1.3 mg/d, 2.6 mg/d, or 3.9 mg/d) or placebo, followed by a 12-week open-label dose-titration period. Safety was evaluated in all patients. Skin reactions at the application site were the most common AEs reported. Erythema was observed in 3.1%, 4.5%, and 5.6% of patients administered 1.3 mg/d, 2.6 mg/d, and 3.9 mg/d oxybutynin TTSs, respectively, compared to 2.3% of patients given the placebo TTS. Pruritus was observed in 10.8%, 13.5%, and 16.8% of patients receiving the respective active treatments, compared to 6.1% of patients given the placebo; 10.2% of patients during the double-blind period and 7.3% of patients during the dose-titration period withdrew from the study. The most common reason cited for withdrawal was skin reaction.³⁷

Rotigotine

Rotigotine is a lipophilic dopamine receptor agonist used to treat Parkinson disease. The TTS is applied once daily and worn continuously for 24 hours.⁴¹

As stated in an article reviewing the use of this drug, local application-site reactions are among the most commonly reported adverse effects. In trials of patients with early Parkinson disease, application-site reactions

occurred more commonly in patients administered a rotigotine TTS than in placebo patients. Most skin reactions were scored as mild (1, minimal erythema); a score of 3 or higher (erythema and papules) was uncommon (the authors did not report numbers of patients with each grade of reaction). In trials for early Parkinson disease, skin reactions occurred in 37 of 649 active-TTS patients (5.7%) and 14 of 289 placebo patients (4.8%). Patients with advanced Parkinson disease had a slightly higher rate of skin reactions: reactions occurred in 31 of 434 patients (7.1%) using the active TTS and in 12 of 219 patients (5.4%) using the placebo. There was no mention of patch testing.⁴¹

Methylphenidate

The methylphenidate TTS is used for treatment of attention-deficit/hyperactivity disorder (ADHD) and can be worn up to 9 hours a day.⁴²

In a randomized open-label single-dose two-way crossover study of the methylphenidate TTS in 27 children diagnosed with ADHD, application of the TTS at the scapula and hip area produced similar skin side effects. Clinicians evaluated the application sites for signs of skin irritation, discomfort, and adhesion. The degree of erythema and edema at the patch sites themselves was assessed before application and 30 minutes after patch removal. While the TTS was in place, the skin adjacent to it was assessed at 2, 4, 8, 12, and 16 hours after application. Erythema and edema were rated independently on a scale of 0 (no erythema or edema) to 4 (severe erythema or edema). The patients assessed their levels of discomfort at the TTS site at 0, 2, 4, 8, 12, and 16.5 hours after patch application. Discomfort was rated on a scale of 0 (no discomfort) to 3 (severe or intolerable). One patient reported a rash; another reported erythema. One boy with a history of environmental allergies withdrew early from the study with a mild rash over his chest and arms that developed during his second treatment period (the site of application was the hip); the rash lasted 10 days and resolved without sequelae. Many hip and scapular sites were judged to have no erythema (43% and 52%, respectively). “Very slight” or “well-defined” erythema was reported slightly more often on the hip than in the scapular area (54.2% and 45.8%, respectively). No discomfort was reported by patients in 97% of hip and 86% of scapular applications. Other skin reactions (including edema) were not reported. In this study of a methylphenidate TTS with a 16-hour wear time, no serious adverse effects were reported. Patch testing was not performed.⁴²

In a multicenter open-label dose-optimization study of a methylphenidate TTS in 305 patients with ADHD, the TTS was applied to alternating hips of children aged 6 to 12 years; it was applied once daily and worn for 9 hours throughout 7 weeks. Assessments included the experience of discomfort and dermal response scale (DRS) scoring from 0 (no irritation) to 7 (strong reaction spreading beyond the test site); additional skin evaluations were performed for patients with DRS scores of 4 (definite edema) or higher. Skin reactions were among the most common adverse effects; 4.6% of patients discontinued the TTS owing to application-site pruritus, and 2.3% discontinued the TTS owing to application-site reactions. Four participants (1%) received a DRS score of 4, and one of these patients (0.3%) was found to be patch test positive to methylphenidate 10% pet, 0.1% pet, 10% aq, and 0.1% aq. No oral rechallenge with methylphenidate was attempted. No participants received a DRS score greater than 4. One subject discontinued the methylphenidate TTS owing to definite edema (a DRS score of 4), itching and burning at both current and past TTS application sites, and urticaria on the abdomen and thighs. The investigator judged the urticaria to be related to the methylphenidate TTS.⁴³

Rivastigmine

The rivastigmine TTS is approved for use as a treatment of mild-to-moderate Alzheimer disease. It is available in two strengths: 4.6 mg per 24 hours and 9.5 mg per 24 hours. In a review of a rivastigmine TTS used in Alzheimer disease, Kurz and colleagues discussed the risk of additional adverse effects not associated with oral administration, such as skin irritation at the application site.⁴⁴ Winblad and Machado reported that erythema is the most common AE, that it was thought to be caused by removal of the patch, and that it generally resolves spontaneously.⁴⁵

During the IDEAL trial (a 6-month randomized double-blind placebo-controlled study of a rivastigmine TTS used in Alzheimer disease), patients were randomized to one of four treatments: rivastigmine capsules (12 mg/d), a 10 cm² rivastigmine TTS (9.5 mg/d), a 20 cm² rivastigmine TTS (17.4 mg/d), and placebo. Skin irritation was assessed by the investigator or caregiver, and most patients experienced “no,” “slight,” or “mild” skin irritation (90–98% across all patch doses). Less than 2.5% of patients in any treatment group discontinued the TTS because of adverse skin reactions.⁴⁶ The signs and symptoms most frequently reported as moderate to severe were erythema (8% for the 9.5 mg/24 h rivastigmine patch vs up to 4% for placebo) and pruritus (7% for the 9.5 mg/d

rivastigmine patch vs up to 3% for placebo).⁴⁶ During the 24-week double-blind phase of the study, 89.6% of patients given the rivastigmine 9.5 mg/d TTS reported “no, slight, or mild” signs or symptoms as their most severe application-site reaction. Erythema and pruritus were the most commonly reported reactions. No patient suffered a skin reaction that was reported as a serious AE. Some patients discontinued using the TTS because of an application-site reaction (2.4% in the target 9.5 mg/d TTS group). There was a 28-week open-label extension that reported skin side effects similar to those of the double-blind phase.⁴⁷ Overall, 3.7% of patients discontinued using the rivastigmine TTS because of application-site skin reactions. The severity of the skin reactions did not worsen over time. No patch testing was reported.⁴⁷

Lefèvre and colleagues conducted a trial to determine the relative pharmacodynamics and tolerability of a rivastigmine TTS applied to various sites on the body. Forty subjects applied a rivastigmine 18 mg TTS to the upper back (reference site), chest, abdomen, thigh, and upper arm. The median time of use was 16 hours for all sites except for the thigh, for which the median time was 22 hours. Each application site was scored for skin irritation before TTS application (0 hours); at the time of TTS removal; and 2, 4, 8, 12, and 24 hours after TTS removal. At 24 hours after removal, the chest or upper arm sites showed no erythema, and only one case each was reported on the abdomen, thigh, and upper back. TTS application on the abdomen and thigh was more likely to result in the development of erythema (odds ratio [OR] 13.7 [CI, 8.4–22.5] for the abdomen; OR 5.9 [CI, 3.7–9.6] for the thigh) than was TTS on the upper back (reference) site. However, applications on the chest and upper arm were less likely to display erythema (OR 0.49 [CI, 0.3–0.8] for the chest; OR 0.35 [CI, 0.2–0.6] for the upper arm). No other skin side effects such as edema or papules were reported. The authors concluded that the application of the rivastigmine TTS to the upper arm, chest, or upper back is less likely to cause erythema than application to the abdomen or thigh.⁴⁸

Investigational TTSs

Nicardipine

Nicardipine is used for treatment of angina and hypertension. Nicardipine is not yet commercially available in a TTS. A study by Krishnaiah and colleagues was undertaken to develop a suitable nicardipine TTS. Six male volunteers

participated in a crossover study with an immediate-release capsule of nicardipine hydrochloride 30 mg and with a 25 cm² nicardipine TTS (with 8% w/w of carvone) applied to the anterior surface of the forearm, near the elbow. At the end of the study (2 days), no local irritation at the TTS application sites was observed.⁴⁹

Teriparatide

Teriparatide is being investigated for use in a transdermal microneedle patch. This medication has historically been delivered by daily subcutaneous injection to treat osteoporosis. The microneedle TTS consists of a 5 cm² adhesive patch with teriparatide coated on a 2 cm² titanium microneedle array of 1,300 microneedles approximately 190 µm in length. The tips of the microneedles were coated with 20 µg, 30 µg, and 40 µg of teriparatide and subsequently dried.

Cosman and colleagues tested the microneedle teriparatide TTS in 165 postmenopausal women. One woman left the study early owing to moderate hyperpigmentation at the application site of a 30 µg TTS. The authors reported no cases of delayed hypersensitivity or skin infection. They reported “a few incidents of edema, punctate bruising, or pinpoint bleeding at the site of administration.” Not surprisingly, all patients experienced transient mild-to-moderate erythema at the application site (with no difference between the placebo and teriparatide TTS groups).⁴

Glipizide

Glipizide is currently being investigated for use in a TTS. A study was performed with a glipizide matrix TTS using combinations of ethyl cellulose/polyvinylpyrrolidone and ammonio methacrylate copolymers (Eudragit RL 100 and Eudragit RS 100, Röhm GmbH & Co. KG, Darmstadt, Germany). Various in vitro and in vivo parameters, including skin irritation, were evaluated in mice. Negligible skin irritation was reported.⁵⁰

Future TTSs

A programmable carbon nanotube membrane TTS for nicotine delivery has been studied in vitro on 200 µm human skin sections harvested during abdominoplasty. The TTS successfully switches between high and low nicotine fluxes. The change in flux could be used to alter the demand levels in nicotine-cessation treatment. These TTSs are programmable and may be useful for single-application long-wear use in nicotine cessation or for other

therapies that require variable or programmable delivery rates. Skin side effects of this device have not been reported.³

Conclusions

New medications are rapidly being incorporated into transdermal therapeutic systems for treatment of many different diseases. There is research into developing novel TTSs with innovative methods of drug delivery, such as the microneedle and carbon nanotube membrane TTSs discussed in this article. It remains important to recognize that skin signs and symptoms are frequently the most common adverse effects associated with TTSs. Patients should be educated in proper application technique, duration of use, and management of skin irritation. They also should be made aware that the TTS is an ideal environment for inducing contact allergy, and they should be advised to seek evaluation by a physician if conservative measures do not result in clearance of their skin symptoms.

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