

Commentary

Practical Management of Cutaneous Reactions to the Methylphenidate Transdermal System: Recommendations from a Dermatology Expert Panel Consensus Meeting

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ABSTRACT

Background: Psychostimulants remain the most-used medications for attention-deficit/hyperactivity disorder (ADHD). The methylphenidate transdermal system (MTS) is the first stimulant patch dosage formulation to be approved by the US Food and Drug Administration for the treatment of the symptoms of ADHD in children aged 6 to 12 years. The MTS patch is approved to be applied once daily to the hip and worn for 9 hours. While cutaneous reactions may occur with any formulation of medication, they are more likely with transdermal administration.

Objective: The purpose of this commentary was to describe the types of cutaneous reactions that have been reported with transdermal systems in general, review the cutaneous adverse events seen in clinical trials with the MTS specifically, and provide practical management suggestions for prevention and treatment of these potential cutaneous reactions.

Methods: In September 2007, a group of child psychiatrists, pediatricians, developmental pediatricians, and pediatric neurologists who treat ADHD and have had experience in their practices with MTS convened to discuss cutaneous reactions in relation to its use. Information collected from this meeting and from the clinical trials database of the sponsor was reviewed by a panel of 3 dermatologic clinical experts in contact dermatitis and 1 pediatric dermatologist. The panel's recommendations form the basis for this report.

Conclusions: Mild to moderate erythema is a common cutaneous effect with MTS use, and is generally not a cause for discontinuation if seen in isolation. Irritant

contact dermatitis is relatively common and can be reduced and treated by alternating patch application sites, moisturizing, gentle skin care, and application of topical corticosteroids at the previous patch sites if needed. Allergic contact dermatitis (ACD) and allergic contact urticaria are rare when MTS is worn as directed in the prescribing information. MTS should be discontinued if ACD is suspected. (*Clin Ther.* 2008;30:326–337) © 2008 Excerpta Medica Inc.

Key words: ADHD, Daytrana, methylphenidate transdermal system, patch, stimulants, cutaneous reactions.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is associated with core symptoms of developmentally inappropriate levels of inattention, hyperactivity, and impulsivity beginning in early childhood and is one of the most common neurobehavioral disorders in children.^{1,2} ADHD affects ~8% of children in the United States,³ of whom an estimated 60% continue to experience symptoms and impairment into adolescence and adulthood.⁴

Treatment data on ADHD support the efficacy of medication and behavioral therapy; however, studies suggest that pharmacologic treatment may be the

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most important variable in a multimodal treatment plan for a successful outcome.^{5,6} For decades, psychostimulant medications have been the mainstay of ADHD pharmacologic management and are the most studied treatments, with >200 randomized controlled trials reporting short-term efficacy of stimulants over placebo.⁷ Consensus guidelines support their use as first-line psychopharmacologic treatment of ADHD, and oral dosage formulations of amphetamine and methylphenidate are the treatments most often used for ADHD.⁸ The methylphenidate transdermal system (MTS)* is the first patch medication approved by the US Food and Drug Administration (2006) for the treatment of ADHD in children aged 6 to 12 years. In general, transdermal therapeutic systems (TTSs) (commonly called “patches”) allow drugs to be delivered in a rate-controlled manner that reduces first-pass metabolism and the fluctuating plasma concentrations encountered with some oral medications.⁹

There are 2 main types of TTSs used commercially: reservoir and matrix.¹⁰ Reservoir TTSs have an active

ingredient with permeation enhancers contained in a liquid depot that is released through a rate-controlling membrane. Matrix TTSs include a single layer of a mixture of the active ingredient, adhesive, and other components that is directly adjacent to the skin; a rate-controlling membrane is not necessary.^{11,12} MTS is a matrix TTS comprising the following elements: a fluoropolymer-coated protective release liner that is removed prior to patch application; an adhesive (DOT Matrix, Noven Pharmaceuticals, Inc., Miami, Florida) layer consisting of acrylic and silicone adhesives and methylphenidate; and an outside backing layer that is exposed to the environment following patch application (Figure 1).¹³

Cutaneous reactions may be seen with TTS delivery and can be irritant or allergic in nature.¹¹ Irritant contact dermatitis (ICD) is by far the most common (~80% of all contact dermatitis)¹⁴ and has less serious potential consequences¹⁴ than allergic reactions (allergic contact dermatitis [ACD] and allergic contact urticaria [ACU]). Each of these 3 types of reactions is considered in more detail in subsequent sections. The purpose of this commentary was to describe the types of cutaneous reactions that have been reported with TTS in general, review the cutaneous reactions seen in

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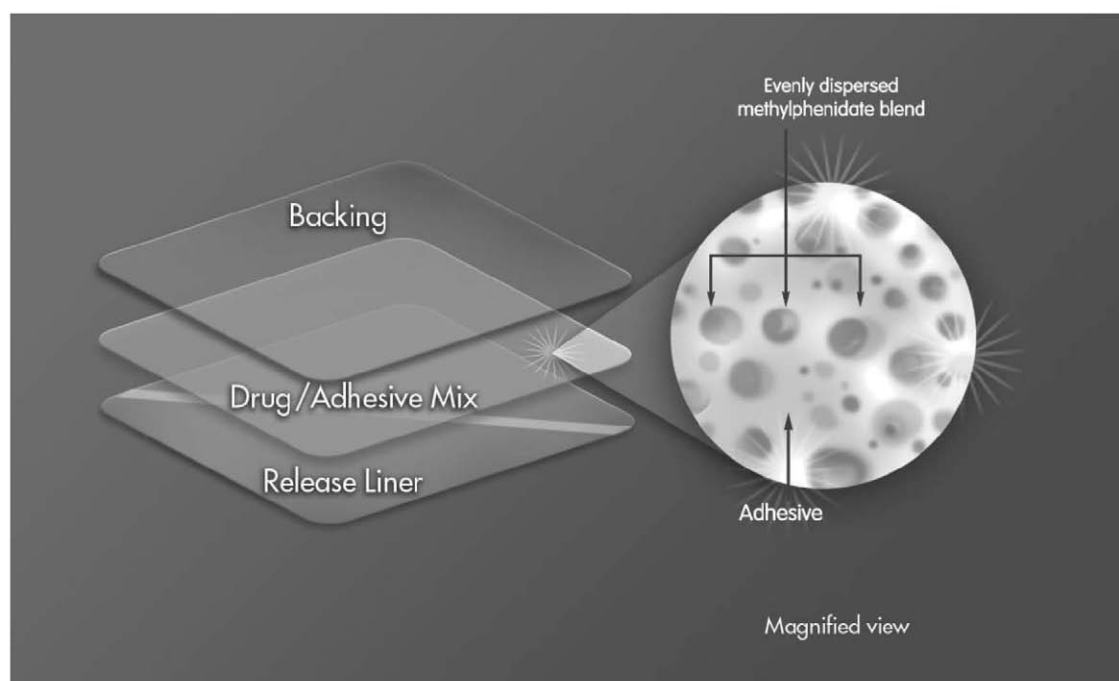


Figure 1. Methylphenidate transdermal system.¹³

clinical trials of MTS specifically, and provide practical management suggestions for the prevention and treatment of these potential cutaneous reactions.

MATERIALS AND METHODS

In September and November 2007, 2 meetings sponsored by the Division of Global Medical Affairs at Shire were convened among specialty physicians from the United States. At the first meeting, 41 participating clinicians (from specialties including child psychiatry, pediatrics, developmental pediatrics, and pediatric neurology) were selected from a larger group of 110 ADHD thought-leaders who attended a North American ADHD Consultants meeting. Clinicians were selected based on their clinical experience in prescribing MTS (all were required to have written ≥ 50 MTS prescriptions or $\geq 10\%$ of their total ADHD prescriptions written for MTS over the previous 12 months). Additionally, they were to have observed cutaneous reactions with the use of MTS. At this first meeting, clinicians discussed the types of cutaneous reactions seen with MTS use in their practices and their current methods of educating patients in the prevention and management of cutaneous reactions seen with MTS use.

The second meeting assembled 3 dermatologic clinical experts in contact dermatitis (E.M.W., J.F.F., and M.J.Z.) and 1 pediatric dermatologist (A.S.P.). Panel members were selected if they had previously served as expert dermatologic consultants in clinical trials of MTS (E.M.W., A.S.P., and J.F.F.) or had been recommended to serve on this panel by >1 other panel member (M.J.Z.). In preparing this commentary, the panel evaluated and discussed: (1) the results from the first consultants meeting; (2) cutaneous reactions reported in the clinical trials database of the sponsor; (3) relevant published literature of cutaneous reactions with TTS use as reviewed by Musel and Warshaw¹¹; and (4) written contributions from the panel members based on their own literature reviews and clinical expertise covering the following: contact dermatitis (irritant and allergic); prevention and treatment of cutaneous reactions associated with TTS; serious cutaneous reactions; and indications of when to discontinue treatment with TTS.

Cutaneous Reactions Reported with Transdermal Systems

Irritant Contact Dermatitis

ICD is a nonimmunologic response of the skin to direct damage. Although the exact prevalence of ICD

is unknown, it is the most commonly reported cutaneous reaction among users of TTS, reported in up to 97% of patients.¹¹ Common irritants include soaps, solvents, abrasives, and adhesives.^{15,16} Clinically, ICD appears as sharply demarcated red patches and/or plaques typically limited to the area of TTS application.¹⁷ ICD usually fades progressively during the several days after patch removal¹⁷; this pattern is often called a “decrecendo” pattern. Desquamation (scaling) may also be observed as the irritation subsides. Patients may report burning, pain, or itching with ICD, but these symptoms are reported as mild in $\sim 95\%$ of cases.^{11,18} Figure 2 depicts 2 examples of ICD in response to patches.

Several factors are thought to play a role in the development of ICD in response to TTS. When any type of TTS is removed, sloughing of cells in the superficial part of the upper layer of the skin (stratum corneum) results in mild skin-barrier disruption.¹⁹ If sites of TTS application overlap, barrier disruption may be cumulative. Cutaneous occlusion by TTS can also obstruct sweat ducts, leading to escape of some sweat from the duct within the skin and secondary inflammation.²⁰ Sweat itself is an irritant and may also be trapped against the skin by the TTS.^{21,22} Differential shear forces (friction at the edge of the TTS from movement of mobile skin surrounding the TTS and immobile skin under the TTS) may also contribute to the risk for ICD.²³ Wearing a TTS may exacerbate the potential irritancy of residual cutaneous contactants, such as soap.²⁴ The routine cutaneous barrier disruption from bathing or showering immediately prior to TTS application may also exacerbate irritation.²⁵ There is no specific diagnostic test for ICD. The diagnosis of ICD is determined by clinical appearance, history, and exclusion of other causes.²⁶

Allergic Reactions

Two types of allergic reactions have been described with TTS use: ACD and ACU. The prevalence of these reactions as related to TTS use is unknown.

Allergic Contact Dermatitis

ACD is a type of T-cell-mediated, delayed, type IV hypersensitivity (eg, poison ivy dermatitis). In ACD related to TTS use, the relevant allergen can be the active drug or an inert component of the TTS. As reviewed by Musel and Warshaw,¹¹ ACD has been reported to range from 0% to 25% in clonidine TTS

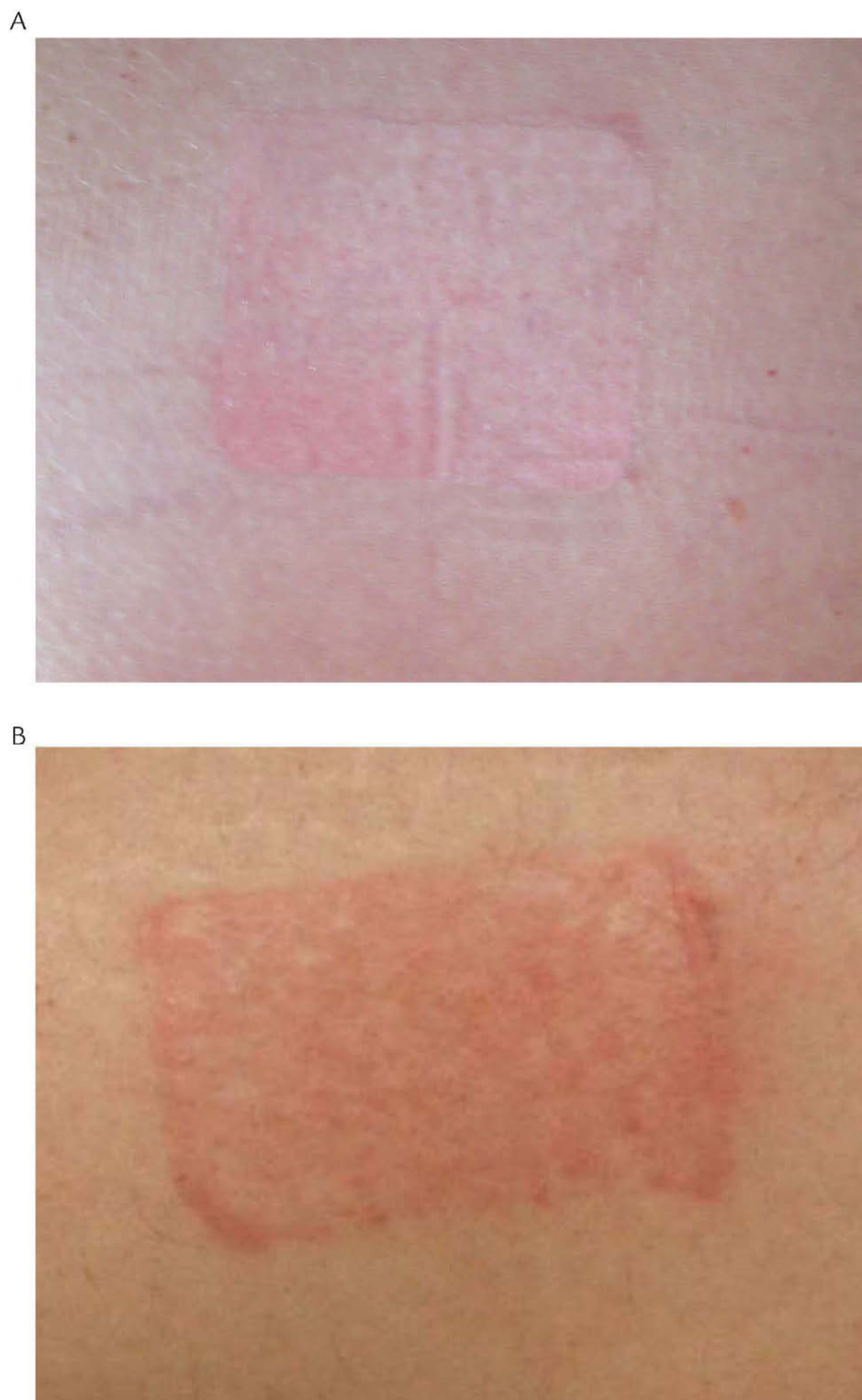


Figure 2. Examples of (A) mild to (B) moderate irritant contact dermatitis from adhesive transdermal therapeutic system application.

trials, up to 3% in nicotine TTS trials, and up to 10% with scopolamine TTS use and has been described in case reports with the use of nitroglycerin, testosterone, estradiol, and fentanyl TTSs. As with any allergic reaction of this type, the first phase in the process is sensitization, a 7- to 14-day process that must occur prior to the development of cutaneous reactivity. Once the allergic reactivity is established, the second phase is elicitation. In elicitation, re-exposure to the allergen leads to ACD within hours to days at sites of recent TTS application.²⁷

Common non-TTS-associated triggers of ACD include poison ivy, nickel (from contact with costume jewelry), and neomycin.²⁸ Clinical features of ACD include redness, swelling, and significant pruritus.^{29,30} In addition, small, fluid-filled vesicles may develop. In contrast to ICD, ACD may spread beyond the borders of the TTS application site (Figure 3).¹¹ ACD is pruritic, often intensely so.³⁰

The natural course of ACD is for complete resolution to occur once the allergen has been removed from contact with the skin. Unlike ICD, which shows a decrescendo pattern after TTS removal, ACD typically shows a “crescendo” pattern; that is, the reaction tends to worsen in the days after TTS removal and may

persist for >3 weeks.^{30,31} Occasionally, re-exposure to the allergen at a new site may result in a flare of dermatitis at the previous site, in addition to ACD at the new site. Table I lists the distinguishing characteristics of ICD and ACD associated with TTS.^{14,30,31} Significant ICD or ACD may leave residual dyspigmentation. It has been the authors' experience that these transient pigmentary alterations do not typically cause scarring and usually resolve spontaneously within 6 to 12 months.³⁰

The diagnosis of ACD is confirmed by identifying the causative allergen via epicutaneous patch testing. This type of testing is usually performed by a dermatologist and involves occlusion of various diluted allergens on the back for 48 hours. The patient then returns a few days later for a delayed reading. A positive reaction usually manifests within 96 hours as a raised, red, palpable, and possibly vesicular plaque at the site of allergen application.^{30,31}

Allergic Contact Urticaria

ACU is a type I immunoglobulin (Ig) E-mediated inflammatory response to a specific allergen. This type of immediate hypersensitivity occurs within minutes of application of the allergen and clinically is charac-



Figure 3. Allergic contact dermatitis reaction to clonidine in a transdermal therapeutic system.

Table I. Distinguishing characteristics of irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD).^{14,30,31}

Characteristic	ICD	ACD
Prevalence	Common	Uncommon
Reaction type	Nonimmunologic	Delayed, type IV cell-mediated hypersensitivity
Concentration	Dependent	Independent
Allergen-triggered	No	Yes
Time to reaction after patch removal	At the time of patch removal	Hours to 7 days after patch removal
Clinical appearance	Sharply demarcated red patches and/or plaques; may be indistinguishable from mild allergic	Often spreads beyond area of exposure; edema or vesicles more likely to be allergic
Course of reaction	Decrescendo: diminishes within several days	Crescendo: often worsens initially; can take up to 3 weeks to resolve
Symptoms	Burning, pain, itching (typically mild)	Itching often intense; sometimes burning/pain
Diagnosis	Clinical course	Epicutaneous patch testing

terized by significant pruritus and the formation of hives (wheals) that may spread beyond the site of the patch. Generalized hives, angioedema, and even anaphylaxis may develop.^{11,31} The most familiar example of ACU is latex allergy.³¹

ACU reactions are much less common than ACD reactions, and there have been case reports with the use of nicotine or nitroglycerin TTS.^{32–34} Diagnosis of ACU is usually confirmed by prick testing (immediate testing, typically performed by an allergist, that involves using a lancet to prick through a drop of diluted allergen into the dermis; a positive reaction occurs within 15 minutes and is defined as a wheal at least half the size of the histamine control) or detection of circulating antibodies (eg, radioallergosorbent test). Table II lists general distinguishing characteristics of ACD and ACU.^{11,30,31}

ACU may be confused with dermatographism, a condition in which pressure or friction against the skin may produce a urticarial or hivelike response.³⁵ Dermatographism is not an allergic reaction and presents as redness and mild swelling from scratching the skin. Predisposed individuals may develop a dermatographic response from the pressure of an adhesive

patch or dressing and/or from the friction that occurs with removal of the patch. Dermatographic responses resolve within minutes or hours.³⁵

Systemic Reactions Related to Contact Allergy

ICD and ACD rarely cause systemic manifestations.¹¹ It is possible that an individual who becomes sensitized to a substance from a cutaneous exposure may develop a reaction (cutaneous or noncutaneous) from systemic exposure to the allergen (systemic contact dermatitis [SCD], also called *systemically reacted ACD*). SCD may take the form of a recurrence of dermatitis in previously affected areas, although more generalized reactions may occur. In contrast to type I IgE-mediated reactions and most systemic drug reactions, SCD is not life-threatening, even if extensive.³⁶ Most patients are able to successfully transition to oral medication after failing TTS therapy due to ACD.^{17,37–44} However, 2 cases of SCD from oral re-exposure after ACD related to the active medication in a TTS have been described with the use of nicotine⁴⁵ and clonidine⁴⁴ TTSs. In both cases, the reactions affected only the skin and subsided after discontinuation of the oral medication. While there have

Table II. Characteristics of allergic cutaneous reactions: Allergic contact dermatitis (ACD) and allergic contact urticaria (ACU).^{11,30,31}

Characteristic	ACD	ACU
Reaction type	Delayed, type IV hypersensitivity	Immediate type I hypersensitivity
Mechanism	T-cell mediated	Immunoglobulin E
Typical allergens	Nickel, neomycin, poison ivy	Latex, fish, seafood, fruit
Systemic reactions	Systemic tolerance	Generalized cutaneous reactions, rhinoconjunctivitis, anaphylaxis

been case reports of ACU related to TTS use,^{32–34} we found no reports of subsequent oral challenge.

Potential Cutaneous Reactions to the Methylphenidate Transdermal System

Irritant and/or allergic reactions to the MTS may occur. In MTS, potential irritants include the adhesive and methylphenidate contained in the matrix layer. Methylphenidate itself is a dermal irritant.^{46–50} Although clonidine-induced ACD after clonidine patch application has been described in up to 25% of patients with suspected ACD,⁵¹ the intrinsic allergenicity of methylphenidate appears to be much lower than that of clonidine, consistent with the low frequency of ACD related to MTS use when it is worn for 9 hours as directed in the prescribing information⁵² (see summary of MTS clinical trials below).

Cutaneous Reactions Observed in Clinical Trials

Data are available from 695 pediatric patients (mean [SD] age, 9.1 [1.9] years) diagnosed with ADHD treated with MTS from 7 completed clinical trials.^{53–59} In these 7 trials, ranging in duration from 4 weeks to 12 months, none of the cutaneous reactions were reported as serious adverse events (AEs), and all were described by investigators as mild (easily tolerated and did not interfere with usual activity) to moderate in intensity (interfered with daily activity but the patient was able to function). There were 6 AEs reported in these studies, and none were related to cutaneous reactions.^{53–59} In addition to the reporting of spontaneous AEs, patients also had Dermal Response Scale (DRS)⁵⁴ and Dermal Discomfort Scale scores⁵⁴ (Tables III and IV) recorded at study visits. In 2 of the 7 trials (n = 58), patients

Table III. Dermal Response Scale.⁵⁴

Score	Definition
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Table IV. Dermal Discomfort Scale.*⁵⁴

Score	Definition
0	No discomfort
1	Mild discomfort
2	Moderate but tolerable discomfort
3	Severe, intolerable discomfort

*Experience of discomfort and pruritus.

applied MTS 1 d/wk^{58,59}; in the other 5 trials^{53–57} (n = 665), patients applied MTS 7 d/wk.^{60–64} In the 2 studies in which 58 patients participated, 28 continued into the long-term extension trial; therefore, 30 patients had no long-term exposure and were not counted among the 665 patients with dermal evaluations.

In the 5 trials with application of MTS 7 d/wk, 623 of 665 (93.7%) MTS-treated patients experienced a maximal DRS score of ≤ 3 (dermal response ranging from no evidence of irritation to erythema and papules) at the current TTS site. Nearly 15% of MTS-treated patients experienced no cutaneous reaction during MTS use: maximal DRS scores in patients evaluated were 0 in 14.3% of patients, 1 to 3 in 79.4%, and ≥ 4 in 5.0%; 9 patients (1.3%) had no DRS data recorded. Thus, more severe cutaneous reactions, leading to discontinuation of use of the patch, were uncommon, as detailed below.

Thirty-one of the 695 patients (4.5%) from the 7 completed clinical trials discontinued treatment due to either an application-site reaction or an application-related AE. The majority (23/31 [74%]) did so with a maximal DRS score of ≤ 3 . The remainder (8/31 [26%]) had DRS scores of 5 (4 patients), 6 (2 patients), or 7 (2 patients). Of the 31 patients who discontinued MTS treatment due to cutaneous reaction, 21 were subsequently treated with oral methylphenidate, and none of these patients experienced an allergic response to oral methylphenidate. Of the remaining 10 patients, 4 subsequently were treated with amphetamine, 2 did not receive further treatment, and 4 had no further follow-up data available.^{62–65}

Dermal Discomfort Scale scores suggested that discomfort experienced with MTS use was generally mild to moderate in nature. Reports of either “no discomfort” or “mild discomfort” at the current patch sites were observed in 73% of patients, whereas 23% reported “moderate but tolerable discomfort,” and 2.9% reported “severe, intolerable discomfort.”

No cases of ACD/ACU were reported in the 7 completed clinical trials, as none of the patients underwent confirmatory testing for allergic sensitization in these trials. However, an open-label, postmarketing clinical trial (n = 309) designed to characterize the dermal response to MTS, including confirmatory testing for allergic sensitization, has been completed. Results from this study, which used a 9-hour wear time as directed in the prescribing information, will be reported in a forthcoming publication. ACD was suspected in 1 pa-

tient (0.3%) in this study; subsequent patch-test evaluations performed by a study dermatologist indicated that sensitization to methylphenidate had occurred. To date, this patient has not had an oral challenge to methylphenidate.⁶⁶

DISCUSSION AND RECOMMENDATIONS

Prevention of Cutaneous Reactions

Cutaneous reactions to MTS may be minimized by educating families about alternating application sites, avoiding irritants, and providing good skin care to maintain the normal skin barrier.^{67,68}

Alternating Application Sites

It is best to develop a rotational system for the area of patch application. The patch should be applied to the hip area once each day, avoiding the waistline because clothing may cause the patch to rub off. New patches are best applied to the alternate hip, with avoidance of a site that was previously occupied by a patch in the preceding 3 days.⁶⁸ Because stretching and flexing can increase the risk for irritation, the upper hip is an ideal site of placement.²²

Maintenance of the Skin Barrier and Avoidance of Irritants

Good skin care techniques may help to prevent irritation.^{29,68} A mild cleanser (eg, Cetaphil®, Aquanil®, Free & Clear™, or CeraVe™ liquid cleansers) can be used on the hips during bathing. Ideally, baths and showers should be limited to 5 to 10 minutes²⁵ and followed immediately by application of emollients to moist skin (eg, Vaseline® petroleum jelly, Aquaphor®, Eucerin® Original Creme, CeraVe™ cream, Cetaphil® cream, Vanicream™).

Occlusion of skin that has recently been exposed to surfactants (soap) increases the risk for dermatitis, even if the soap is removed before patch application.⁶⁹ Therefore, a bath or shower to cleanse (and remove adhesive) is best taken in the evening, and the patch applied in the morning. The area should be visibly clean; washing with soap immediately prior to MTS application should be avoided. Given the known potential for irritation and impaired skin barrier from isopropyl alcohol (ie, rubbing alcohol) or acetone (as in nail-polish or adhesive removers),^{70,71} wiping the site with these chemicals should be avoided. Similarly, moisturizers should not be applied immediately before MTS application so that good adhesion is ensured.⁶⁸

Patches should be removed gently, and scrubbing of the site to remove any residual adhesive should be avoided. An oil-based product (eg, petroleum jelly, olive oil, mineral oil) can be used to loosen any residual adhesive; nonmedical adhesive removers or acetone-based products should not be applied to the skin.⁶⁸

Treatment of Cutaneous Reactions

Caregivers and patients should be educated that mild to moderate erythema may be seen at the time of patch removal and has been reported in clinical studies. Mild to moderate erythema in isolation can be managed by alternating application sites, avoiding irritants, and using good skin care techniques.⁶⁸ Clinical experience indicates that mild to moderate erythema is generally not a cause for discontinuation if seen in isolation. If erythema does not significantly improve within 48 hours after patch removal, evaluation by the prescribing physician or a dermatologist should be sought.

As described earlier, ACD from MTS has been rarely reported when the patch is worn as directed in the prescribing information,⁵² but several clinical features, in addition to erythema, should raise the suspicion that an individual has become allergic to the patch (Table I).^{29–31} Of note, the features most suggestive of ACD are significant itching, crescendo reaction pattern, presence of vesicles and edema, and extension of the reaction beyond the borders of the patch. Features that are more reassuring that a reaction is ICD include a well-defined, sharp border to the reaction that correlates with the edge of the patch, decrescendo pattern (decrease in redness within 48 hours after removal of the patch from a given site and significant resolution within 7 days), and intermittent occurrence of the irritation. If symptoms consistent with an allergic reaction to the patch develop, the MTS should be discontinued. If confirmation of a diagnosis of contact sensitization (ACD) is necessary, further evaluation by a dermatologist is recommended.

Treatment of MTS-Associated Irritant Contact Dermatitis

Use of emollients may provide temporary relief for irritant reactions at previous patch application sites. If signs or symptoms of an ICD are bothersome and unresponsive to emollients, twice-daily application of a topical corticosteroid of low potency (1.0%–2.5% hydrocortisone ointment) or low-medium potency (des-

onide 0.05% or alclometasone 0.05% ointment) may be considered in addition to the emollient regimen.^{72,73} Application of calamine is not recommended because of its drying properties. Continuous application of corticosteroids at the same site without resolution for >3 weeks should be avoided. Patients or caregivers should not apply topical corticosteroids to the intended patch site immediately prior to patch application because the effects of topical corticosteroids on patch adhesion or methylphenidate absorption have not been established. The potential AEs associated with topical corticosteroid use during treatment with MTS are unknown.

Treatment of MTS-Associated Allergic Cutaneous Reactions

Discontinuation of MTS use is the most crucial component of treatment of MTS-related ACD.^{74,75} After discontinuation, treatment with a medium-strength to potent topical corticosteroid ointment applied twice daily while the dermatitis is active should be considered. A dermatologist can be consulted for further management and epicutaneous patch testing. Application of emollients should be continued; the combination of moisturizer/barrier cream plus corticosteroid has been found to be more effective than the application of steroid or moisturizer alone in studies of nickel-related ACD.^{76,77} Administration of a systemic corticosteroid is typically not necessary. Sedating antihistamines (eg, hydroxyzine, diphenhydramine) may be administered in the evening to decrease nighttime pruritus.³⁰ Sun protection of affected sites also is helpful (and relatively easy for the hip area). If there is a concern about an allergic reaction to methylphenidate (type I or IV), either an alternative medication for ADHD or administration of oral methylphenidate in a supervised medical setting should be considered.

CONCLUSIONS

Mild to moderate erythema is a cutaneous reaction commonly seen with MTS use and is not generally a cause for discontinuation if it occurs in isolation. The incidence and severity of skin irritation with MTS use may be reduced and treated by alternating patch application sites; moisturizing after bathing; gentle skin care (avoidance of irritants such as soap and adhesive removers); and, if needed, application of topical corticosteroids at previous patch application sites. ACD and ACU have been rarely reported when MTS was

worn as directed in the prescribing information. If ACD is suspected, MTS use should be discontinued.

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