

Methylphenidate Patch-Test Protocol and Irritancy Threshold Determination in Healthy Adult Subjects

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Background: The methylphenidate transdermal system (MTS) (Daytrana [Shire Pharmaceuticals Ireland Ltd., Wayne, PA]) has been shown to be well tolerated and effective; however, skin reactions, typically redness and itching, have also been noted with MTS use.

Objective: The purpose of this study was to determine the irritancy threshold of methylphenidate (MPH), the active ingredient in the MTS, in healthy adults for use in subsequent patch testing.

Methods: This was an open-label single-site pilot study. Eligible subjects had MPH (six different concentrations in two vehicles) patch tests applied to the paraspinous region of the upper back. Subjects returned after 48 hours and 96 hours for investigator assessments of each reaction.

Results: All enrolled subjects ($n = 20$) completed the study. There were no definite positive reactions in any subject at any test concentration. Overall, doubtful (macular erythema) reactions were noted on 12 sites at the 48-hour reading and on 6 sites at the 96-hour reading. With both aqueous and petrolatum vehicles, more doubtful reactions were noted at the lower MPH test concentrations.

Conclusion: When performing patch testing to confirm possible allergic contact dermatitis from topical MPH, several test concentrations in the low-to-middle range (such as 0.1%, 1%, and 10%) prepared in petrolatum are advisable.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a neurobehavioral syndrome associated with genetic and environmental risk factors^{1,2} that current diagnostic classifications and criteria define as being associated with a persistent pattern of problematic behavioral characteristics including inattention, hyperactivity, and impulsivity.³ ADHD is one of the most prevalent psychiatric disorders of childhood, affecting approximately 8% of children in the United States⁴; of these, an estimated 60% will continue to experience symptoms and impairments into adolescence and adulthood.⁵

Treatment of ADHD symptoms should involve a comprehensive program that may include medication therapy and psychological, educational, and social interventions. Medication may not be indicated for all children with this syndrome.^{6,7} Of the pharmacotherapy treatment options, current consensus in the United States recommends

a psychostimulant, such as methylphenidate (MPH), as first-line therapy.^{6,8,9} Prior to the April 2006 US Food and Drug Administration's approval of an MPH transdermal system (MTS) (Daytrana, Shire Pharmaceuticals Ireland Ltd., Wayne, PA) for children aged 6 to 12 years with ADHD, MPH was available only in oral formulations. The MTS uses DOT Matrix (Noven Pharmaceuticals, Inc., Miami, FL) technology to create a diffusion-based patch that delivers MPH through the skin with a reduction of first-pass metabolism and the fluctuating plasma concentrations encountered with oral medications.¹⁰ The MTS was specifically formulated to mimic the later pharmacokinetic profile of CONCERTA (McNeil Pediatrics, Titusville, NJ), allowing for once-daily dosing and efficacy throughout the day. Transdermal delivery of MPH is a treatment option for children with ADHD who would benefit from a tailored duration of effect.¹¹

Local irritation is common with transdermal delivery systems, and sensitization to the pharmacologic agent has been reported with some patches.^{12,13} Up to 61% of MTS-treated subjects had a maximal current dermal response scale (DRS) score of 2 (definite erythema) or greater, although the characterization of the skin irritation and the extent of potential sensitization remain unclear. Although allergic contact sensitization associated with the MTS has been suspected in postmarketing reports,¹⁴ previous reports of

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allergic contact sensitization were not evaluated with epicutaneous patch testing; therefore, allergic contact sensitization was never confirmed. The purpose of this study was to determine, for use in subsequent patch testing, the irritancy threshold of MPH (the active ingredient in the MTS) in healthy adults. Concentrations of MPH used in patch testing must be below the irritant threshold to clearly discern allergic contact sensitization from local skin irritation.

Methods

Study Population

Eligible subjects were male or female healthy adults aged 18 years or older who had adequate space on the upper back to apply 12 Finn Chamber patches (Allerderm, Petaluma, CA) and who were able to understand informed consent and comply with all study requirements.

Prospective subjects were excluded if they (1) had a history of sensitivity to MPH, aluminum, or petrolatum; (2) had active dermatitis or another skin condition that, in the opinion of the investigator, could interfere with assessments; (3) had any significant medical conditions that could compromise immune responsiveness (eg, acquired immune deficiency syndrome, lymphoma, other immunodeficiency); or (4) were pregnant or lactating. Prospective subjects affected with alcoholism, drug dependency, mental dysfunction, or other factors that would limit compliance with the study or interfere with regular visits were also excluded from the study.

Prohibited was the use of (1) systemic immunomodulating therapy (corticosteroids, immunosuppressive agents, cytostatics, pentoxifylline, or other medications that, in the opinion of the principal investigator, could affect cutaneous response to irritation) in the 2 weeks prior to participation; (2) intramuscular steroids in the last month; (3) topical steroids, tar, or topical immunomodulating agents on the subject's back in the last 7 days; or (4) phototherapy (ultraviolet B, or psoralen plus ultraviolet A) in the 2 weeks prior to participation.

Subjects provided written informed consent before any study procedures were performed. The institutional review board at the study site approved all study documentation, including the protocol and the informed consent and assent documents.

Study Design and Preparation of MPH Patch Tests

This was an open-label single-site pilot study, and subjects were blinded as to the concentrations on each patch. The

concentrations of MPH, prepared in a compounding pharmacy (Louisville Pharmacy, Louisville, KY) for use in the study, are listed in Table 1. These concentrations were based on the allergen concentrations of other oral medications used in patch testing, the MPH concentrations used in preclinical testing, and the MPH concentration used in the commercial patch.

MPH patch tests (six different concentrations in two vehicles, as listed in Table 1) were prepared in 8 mm aluminum Finn Chambers by expressing 0.05 mL aliquots (measured with 1.0 mL tuberculin syringes for the allergens in petrolatum and with a micropipette for the allergens in aqueous solution) onto each Finn Chamber. The filled chambers were attached to a proprietary adhesive tape (Scanpor, Norgesplaster A/S, Vennesla, Norway) for application directly to the paraspinous region of the upper back, adjacent to the vertebrae.

Study Visits

Prospective subjects who met study inclusion criteria were scheduled for an initial visit. Informed consent, demographic information, and relevant medical history for each subject were recorded at this initial visit. MPH patch tests were applied to the paraspinous region of the upper back. Each patch test was anchored on the lower end and was slowly rolled up the back, pushing out the remaining air.

Because moisture can remove ink markings or cause skin patches to become loose, subjects were instructed to avoid taking showers, splashing water on the patch-test sites when washing their hair, and participating in activities that resulted in excessive perspiration for the study's duration. Subjects were directed not to attempt to replace a skin patch should it detach because this would cause mixing of the chemicals and inaccurate results. Subjects were instructed instead to remove the loose strip, noting the day and time as well as any reactions noticed as the tape was removed, and to mark the area of skin formerly occupied by the removed patch with an ink pen.

Table 1. Methylphenidate Patch-Test Concentrations and Vehicles

<i>Petrolatum</i>	<i>Aqueous</i>
20%	20%
10%	10%
5%	5%
1%	1%
0.1%	0.1%
0.01%	0.01%

Last, subjects were told to contact their doctor if they experienced any pain or itching at the patch site.

The second visit took place approximately 48 hours after the initial visit. At this time, the patches were removed, and the sites were examined. After a 30-minute waiting period, reactions were graded as follows, according to standard North American Contact Dermatitis Group guidelines: 0 = no reaction; 0.5 = doubtful reaction (faint erythema with no induration); 1 = mild reaction (erythema, induration, with or without papules); 2 = moderate reaction (erythema, induration, papules, vesicles); 3 = severe reaction (intense erythema, induration, coalescing vesicles, bullae, spreading).¹⁵ A grade of 2 or 3 suggests a definite allergic reaction, a grade of 1 suggests a possible allergic or irritant reaction, and a grade of 0.5 suggests a mild nonspecific irritant reaction. The investigator did not perform the reading until all patch-test materials were removed and was not shown the patch-test placement key, thus ensuring investigator blinding.

At the third visit, approximately 96 hours after the first visit, reactions were again graded according to the above guidelines. Photographs were taken of representative patch-test reactions.

Results

Twenty female subjects were enrolled in the study, and all 20 completed the study. No subject reported an adverse event during the course of the study. MPH patch-test results are presented in Table 2. There were no definite positive reactions on any subject at any test concentration in either vehicle. Overall, doubtful reactions were noted on

12 sites at the 48-hour reading and 6 sites at the 96-hour reading. Eight subjects showed a doubtful reaction at one or more test sites at the 48-hour reading. At the 96-hour reading, six of these eight subjects showed no reactions; the other two had persistent doubtful reactions. Two subjects showed no reactions at 48 hours but had doubtful reactions at 96 hours. At the 48- and 96-hour readings, doubtful reactions were more commonly reported for MPH in the aqueous test vehicle (4 of 6 concentrations and 3 of 6 concentrations at the 48- and 96-hour readings, respectively) than for MPH in the petrolatum test vehicle (2 of 6 concentrations and 1 of 6 concentrations, respectively). With both aqueous and petrolatum vehicles, more doubtful reactions were noted at the lower MPH test concentrations.

Only two of the subjects (subjects 7 and 10) had a history of atopic dermatitis. At 48 hours, subject 7 showed a doubtful reaction at the 0.1% aqueous site and subject 10 showed a doubtful reaction at the 0.01% petrolatum site. All patch tests were negative at 96 hours in these subjects.

Discussion

In the event a patient presents for patch testing because of a possible allergic skin reaction to an MTS, it is important to know the irritant threshold of MPH to ensure that the concentration is not itself irritating. Although the aqueous vehicle showed more doubtful irritant reactions than the petrolatum vehicle, neither vehicle at any concentration showed any significant true irritant or allergic response. This suggests that, in these vehicles, MPH up to a 20% concentration did not cause irritant patch-test reactions.

Table 2. Methylphenidate Patch-Test Irritancy Threshold Results

MPH Concentration and Vehicle	Subjects Tested (N)	Subjects with Positive Reading at 48 Hours (N)	Subjects with Positive Reading at 96 Hours (N)	Subjects with Doubtful Reading at 48 Hours (N)	Subjects with Doubtful Reading at 96 Hours (N)
20% pet	20	0	0	0	0
10% pet	20	0	0	0	0
5% pet	20	0	0	0	0
1% pet	20	0	0	0	0
0.1% pet	20	0	0	1	0
0.01% pet	20	0	0	2	1
20% aq	20	0	0	2	2
10% aq	20	0	0	0	0
5% aq	20	0	0	0	1
1% aq	20	0	0	2	0
0.1% aq	20	0	0	2	0
0.01% aq	20	0	0	3	2

aq = aqueous; MPH = methylphenidate; N = number of subjects; pet = petrolatum.

It is unclear why more doubtful reactions at the lower concentrations were observed. A possible reason may involve the patch-test placement on the back. The lower MPH concentrations were placed on the lower part of the test strips. There may have been tighter adhesion of the patches at these sites, allowing some irritation from the patch-test chambers or test material, which showed up as a doubtful irritant reaction.

Although the results are generalizable only to adult female subjects, based on the enrolled population, the lack of any significant irritant reactivity suggests that (1) MPH may be less bioavailable in these patch-test preparations than in the MTS, (2) significant irritation may be elicited only after repeated application of MTS to the same site, or (3) perhaps the MTS adhesive matrix, by itself or synergistically with MPH, is a primary cause of irritant reactions in patients treated with the MTS. Transdermal delivery of MPH with the DOT Matrix technology used in the MTS may be different than with the vehicles used for patch testing. Further studies that control for these variables may provide additional information about the irritancy threshold of topical MPH, the active ingredient in the MTS.

Conclusion

On the basis of the results of this pilot study, any of the test vehicles and concentrations should be nonirritating in diagnostic patch testing. When testing individual patients who have had a putative allergic contact dermatitis from methylphenidate (the active ingredient in the methylphenidate transdermal system), the use of several test concentrations in the low-to-middle range (such as 0.1%, 1%, and 10%) is suggested. Because more low-grade irritant reactions were seen with the aqueous vehicle and since the aqueous vehicle is more technically difficult to apply to the test patches, petrolatum is the vehicle of choice. In the future, it may be possible to further refine these recommendations if patients with true allergic reactions can be identified and patch-tested.

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