Chemical Leukoderma Associated with Methylphenidate Transdermal System: Data From the US Food and Drug Administration Adverse Event Reporting System

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Objective To identify and characterize cases of chemical leukoderma, an underrecognized adverse event, associated with the methylphenidate transdermal system (MTS) reported to the US Food and Drug Administration Adverse Event Reporting System (FAERS).

Study design We searched the Food and Drug Administration Adverse Event Reporting System for reports of chemical leukoderma associated with MTS, received by the Food and Drug Administration from April 6, 2006 to December 23, 2014.

Results We identified 51 cases of chemical leukoderma reported with the use of MTS. The median age was 11 years; 43 cases reported leukoderma at or near the application site only, and 7 reported leukoderma at other parts of the body in addition to the application site; 1 case did not provide enough information to confirm the affected site. The time to onset ranged from 2 months to 4 years after the initiation of MTS. MTS was discontinued in 31 cases. Thirteen patients were prescribed treatment for repigmentation. Three cases reported continued spread of leukoderma after MTS was discontinued. Nineteen cases were diagnosed as vitiligo, including 5 cases reporting histologic features consistent with vitiligo. Leukoderma was persistent in all cases. The median follow-up interval after the discontinuation of MTS in 23 cases was 14 months.

Conclusions As outlined in recent changes to the prescribing information for MTS, health care professionals need to be aware of the potential risk of chemical leukoderma caused by MTS, especially given that chemical leukoderma is often misdiagnosed as idiopathic vitiligo. MTS should be discontinued at the earliest sign of pigment loss and other treatment options considered. *(J Pediatr 2017;180:241-6).*

Chemical leukoderma is an acquired depigmentation or hypopigmentation caused by repeated application of or exposure to a specific chemical that is toxic to epidermal melanocytes. This condition was first described by Oliver et al[1] as occupational leukoderma when rubber gloves that contained monobenzyl ether of hydroxyquinone caused skin depigmentation at the site of contact. Over the years, this condition has also been termed occupational vitiligo, occupational leukoderma, contact leukoderma, and chemical depigmentation until Hogan[2-6] first used the term chemical leukoderma in 1992. Ghosh and Mukhopadhyay[7] published a definitive article in 2009 using the term chemical leukoderma, and this is now the more widely accepted term.

Chemical leukoderma is often misdiagnosed as idiopathic vitiligo. The histologic findings are similar in chemical leukoderma and vitiligo; the main finding is a scarcity or absence of melanocytes. As a result, the diagnosis is made usually on clinical grounds. The diagnosis of chemical leukoderma must include 3 of the following 4 criteria: (1) acquired vitiligo-like depigmented lesions, (2) history of repeated exposure to a specific chemical compound, (3) patterned vitiligo-like macules conforming to site of exposure, and (4) confetti macules. Occasionally, there may be distant spread of the depigmented lesions in addition to the site of contact.[8]

A wide variety of chemical products have been identified as causes, including monobenzyl ether of hydroquinone, adhesives, insecticides, and industrial chemicals. Prevention is the most important aspect of management, and further exposure to the offending agent must be avoided once the diagnosis is suspected. The depigmentation is generally persistent and may occasionally progress even after contact with the offending agent is discontinued.[9] Spontaneous recovery may occur, but is not the norm, and treatment, as for vitiligo, is usually required.

ADHD	Attention deficit-hyperactivity disorder
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
MTS	Methylphenidate transdermal system

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Daytrana (methylphenidate transdermal system [MTS]; Noven Pharmaceuticals, Inc, Miami, Florida) is a patch indicated for the treatment of attention deficit-hyperactivity disorder (ADHD). MTS is an extended-release formulation administered once daily. MTS is currently the only ADHD medication available as a patch in the US, which offers an additional treatment option in young patients who cannot swallow pills.

Some of the most commonly reported adverse reactions in clinical trials with MTS included the well-known adverse reactions that occur with orally administered methylphenidate. In clinical trials, the majority of the subjects, in both the treatment and placebo groups experienced erythema at the application site. However, a higher proportion of subjects in the active methylphenidate group had dermal application site reactions, and there was generally a higher level of severity of application site reactions in the methylphenidate group. Methylphenidate is a chemical irritant. Discoloration, hyperpigmentation, and hypopigmentation are among some of the application site reactions reported postmarketing that are included in the current prescribing information.[10] Reports of vitiligo associated with MTS stimulated a review of all cases of application site hypopigmentation or depigmentation.

Methods

We searched the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database for postmarketing reports of chemical leukoderma associated with MTS received by the FDA from April 6, 2006 (US approval date) to December 23, 2014. FAERS is a computerized repository of spontaneous adverse event reports submitted by product manufacturers, consumers, and health care professionals from US and non-US sites.[11] The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.[12] MedDRA is the international medical terminology developed by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

To identify cases of chemical leukoderma, we searched the FAERS database using the following MedDRA Preferred Terms: application site discoloration, application site pallor, hypopigmentation of eyelid, leukoderma, pigmentation disorder, postinflammatory pigmentation change, skin depigmentation, skin discoloration, skin hypopigmentation, and vitiligo. We included cases describing leukoderma (skin hypopigmentation or depigmentation), at or near the application site of the MTS.

To evaluate the cases, we calculated a time to onset and follow-up interval. The time to onset of chemical leukoderma was calculated from the MTS initiation date to the finding or diagnosis of the loss of skin pigmentation, whichever was earlier. For cases that reported a discontinuation of MTS and no resolution of leukoderma, a follow-up interval was calculated to evaluate the persistence of chemical leukoderma after the discontinuation of MTS. The follow-up interval was calculated from the MTS discontinuation date to the latest date that the manufacturer or the FDA received the report. If the manufacturer submitted the report to the FDA, we calculated the follow-up interval using the latest date that the manufacturer received the report. If the FDA received the report directly from a consumer or health care professional, we calculated the follow-up interval using the latest date that the FDA received the report.

Results

We identified 51 cases that met our inclusion criteria; 43 patients had chemical leukoderma localized to the application site only; 7 patients had leukoderma in other parts of the body in addition to the application site; and the remaining case lacked sufficient information to determine whether there was distant spread in addition to the application site. Seven cases reported the finding of leukoderma when the application site did not tan. Although some cases described the leukoderma as the shape and size of the MTS, other cases reported the size of the leukoderma area was larger than the patch, measuring up to 8 inches in diameter. Nineteen cases were reported as vitiligo, 12 of whom were seen by a dermatologist, and 5 had skin biopsies reported as consistent with vitiligo. Four additional patients were evaluated by a dermatologist, of whom 1 had a skin biopsy; in these cases, it was not reported that the patients were diagnosed with vitiligo. Six cases reported that patients, aged 8 to 13 years old, suffered from "embarrassment," "fear," or "emotional trauma" as a result of the persistent leukoderma. In addition, these cases reported that leukoderma made participation in sports and other childhood activities difficult.

The characteristics of the 51 cases is presented in the **Table**. Of the 40 that reported an age, all but 1 case reported an age of 16 years or younger. The mean age was 11 years old. Of the 49 cases that reported the sex of the patient, 59% were male and 51% were female. The race was reported in only 21cases; all but one of the patients were Caucasian. All strengths of the MTS (10 mg, 15 mg, 20 mg, and 30 mg patches) were associated with chemical leukoderma in the 38 cases that reported a dose. Only 20 cases provided enough information to calculate a time to onset, which ranged from 2 months to 4 years after the initiation of MTS. Nineteen additional cases provided an estimate only for the time to onset.

None of the cases reported resolution during follow-up, despite discontinuation of MTS or treatment for repigmentation. Thirty-one patients discontinued the use of MTS, and 16 patients reported continued use of the patch. It is unknown whether the MTS was continued or discontinued in 4 cases. Thirteen patients were prescribed treatment for repigmentation. Twelve patients received treatment with 1 or more of the following: topical corticosteroid, topical calcineurin inhibitor, and phototherapy; 1 patient was prescribed an unspecified medication. Of the 13 cases that reported treatment, MTS was