

Transdermal Rivastigmine

Management of Cutaneous Adverse Events and Review of the Literature

Jill Greenspoon,¹ Nathan Herrmann^{2,3} and David N. Adam^{4,5}

- 1 Faculty of Medicine, University of Western Ontario, Schulich School of Medicine and Dentistry, London, ON, Canada
- 2 Faculty of Medicine, University of Toronto, Toronto, ON, Canada
- 3 Division of Geriatric Psychiatry, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
- 4 Faculty of Medicine, University of Toronto, Toronto, ON, Canada
- 5 St. Michael's Hospital, Toronto, ON, Canada

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Abstract

Alzheimer's disease is a chronic neurodegenerative disorder resulting in part from the degeneration of cholinergic neurons in the brain. Rivastigmine, a cholinesterase inhibitor, is commonly used as a treatment for dementia due to its ability to moderate cholinergic neurotransmission; however, treatment with oral rivastigmine can lead to gastrointestinal adverse effects such as nausea and vomiting. Transdermal administration of rivastigmine can minimize these adverse effects by providing continuous delivery of the medication, while maintaining the effectiveness of the oral treatment. While the transdermal form of rivastigmine has been found to have fewer systemic adverse effects compared with the oral form, cutaneous reactions, such as contact dermatitis, can lead to discontinuation of the drug in its transdermal form. Lack of patient compliance with regard to applying the patch to the designated site, applying the patch for the correct length of time or rotating patch application sites increases the risk of cutaneous adverse reactions. This article outlines the diagnosis and management of irritant contact dermatitis and allergic contact dermatitis secondary to transdermal rivastigmine.

The large majority of reactions to transdermal patches are of an irritant type, which can be diagnosed clinically by the presence of a pruritic,

erythematous, eczematous plaque strictly confined to the borders of the patch. In contrast, an allergic reaction can be differentiated by the presence of vesicles and/or oedema, erythema beyond the boundaries of the transdermal patch and lack of improvement of the lesion 48 hours after removal of the offending treatment. By encouraging the patient to follow a regular rotation schedule for the patch, and using lipid-based emollients for irritant dermatitis and pre- and post-treatment topical corticosteroids for allergic dermatitis, cutaneous reactions can often be alleviated and patients can continue with their medication regimen. Other simple changes to a patient's treatment routine, including minimizing the use of harsh soaps, avoiding recently shaven or damaged areas of skin and carefully removing the patch after use, can help to further decrease the risk of dermatitis development.

Alzheimer's disease is a chronic neurodegenerative condition characterized by disturbances in cognition, daily function and behaviour. These progressive symptoms result in part from degeneration of cholinergic neurons in the brain. This degeneration leads to decreased levels of the neurotransmitter acetylcholine, which plays a major role in the development of disease symptoms.^[1] Rivastigmine is a cholinesterase inhibitor commonly used as treatment for mild to moderate dementia associated with Alzheimer's disease. Rivastigmine inhibits the hydrolysis of acetylcholine, thus prolonging its action at synapses, and maximizing its action.^[2] While there are three cholinesterase inhibitors in common use, only rivastigmine is available as a transdermal patch; however, a weekly transdermal donepezil patch is currently being reviewed by the US FDA for the potential treatment of mild, moderate and severe Alzheimer's disease.^[3] The transdermal delivery of the drug potentially decreases gastrointestinal adverse effects, though severe cutaneous reactions can in some cases lead to discontinuation of the medication. We review the management of local adverse events associated with transdermal rivastigmine, and outline a guide to the optimum management of these reactions.

1. Clinical Use of Transdermal Rivastigmine

The efficacy of oral rivastigmine in the treatment of mild to moderate Alzheimer's disease symptoms has been well established in >3000 patients

via several double-blind, placebo-controlled clinical trials.^[4,5] However, adverse effects have been noted, with the most common being nausea (23%) and vomiting (17%).^[4] These symptoms, and other gastrointestinal disturbances, are thought to be triggered by rapid peaks and troughs in acetylcholine levels in the brain.^[6] Other adverse effects reported include headache, dizziness, fatigue, sweating, allergy, hypertension, haemorrhoids, falls, hypotension, constipation, confusion, orthostatic hypotension and decreased appetite.^[4-7]

The IDEAL (Investigation of transDermal Exelon® in ALzheimer's disease) trial was a randomized, double-blind, double-dummy, multicentre, placebo- and active-controlled study in which participants were randomized to placebo or to one of three active treatment groups as follows: rivastigmine 9.5 mg/24 hour patch, rivastigmine 17.4 mg/24 hour patch or rivastigmine 12 mg/day capsules. The goal of the study was to investigate the efficacy, safety and tolerability of the transdermal patch compared with oral rivastigmine.^[7] 1195 patients aged 50–85 years with a diagnosis of Alzheimer's disease were included in the study. Compared with the placebo-treated patients, all rivastigmine groups had significantly higher scores on the primary efficacy measures, the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) subscale and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). The incidence of adverse events with the rivastigmine 17.4 mg/24 hour patch was not significantly different from the rivastigmine capsule group; however, it was significantly in-

creased compared with placebo and the rivastigmine 9.5 mg/24 hour patch. The rivastigmine 9.5 mg/24 hour patch showed equivalent efficacy to the rivastigmine 12 mg/day capsule, with a decreased incidence of adverse events.^[7]

Unlike oral rivastigmine, which has two distinct peaks/troughs of cholinesterase inhibition (correlating to the twice-daily dosing regimen),^[8] transdermal administration provides a smoother, more continuous reduction in CNS cholinesterase activity.^[9] With the continuous delivery of drug, the rivastigmine 9.5 mg/24 hour patch has shown an approximately 67% reduction in nausea (7.2% vs 23.1%) and vomiting (6.2% vs 17.0%)^[7] compared with oral dosing, with no diminution in efficacy.

In general, transdermal drug delivery bypasses gastrointestinal and first-pass metabolism, thus it increases drug bioavailability. It also allows for a controlled drug input rate into the bloodstream, which helps avoid toxic or sub-therapeutic doses, and minimizes peaks and troughs in medication concentrations.^[9]

Furthermore, rivastigmine has a number of chemical properties that make it particularly well suited to transdermal delivery. The low molecular mass and amphipathic structure of rivastigmine allow the drug to readily pass through the skin, enter the bloodstream and cross the blood-brain barrier.^[10] Additionally, the potency of rivastigmine allows the transdermal patch to be small, which increases skin tolerability and is more discreet, potentially leading to improved patient compliance.^[11] In the Alzheimer's disease population, transdermal patches may increase patient compliance by providing a visual reminder, which can include the date and time of application written on the patch, of the medication that has been taken, and by making administration easier for caregivers dealing with challenging patients.^[12]

2. Skin Tolerability of Transdermal Rivastigmine

The transdermal Exelon[®] Patch (rivastigmine; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) is composed of a four-layer laminate containing the backing, drug matrix,

adhesive matrix and overlapping release liner, which is removed prior to use. The excipients within the patch include acrylic copolymer, polybutylmethacrylate, polymethylmethacrylate, silicon adhesive, silicon oil and vitamin E.^[13] The patch employs matrix technology, which commonly leads to better skin tolerability than older patch types, due to the absence of a solvent adjunct required for dissolving the active component.^[9] The matrix controls the rate of drug release from the skin, and avoids accidental increased release upon initial patch application, which can be a toxic adverse effect of other patch types.^[9] The amount of drug delivered from the patch is proportional to its surface area in contact with the skin.^[14] The patch is waterproof, which allows the patient to minimize changes to their current cleansing routine.

Common to all medical patches, skin reactions have been associated with the use of the transdermal rivastigmine patch.^[15] In the IDEAL trial, investigators used a 5-point rating system (ranging from no reaction through to slight, mild, moderate and severe irritation) to regularly evaluate skin irritation associated with transdermal rivastigmine. The large majority of patients (89.6%) in the rivastigmine 9.5 mg/24 hour patch group experienced no, slight or mild skin reactions.^[7] 7.6% of patients had moderate or severe erythema, with 2.5% of patients stating skin reaction as the reason for their discontinuation of treatment.^[7] Patients in the 17.4 mg/24 hour patch group had a similarly low withdrawal rate due to skin reaction of 2.3%; however, the percentage of patients with moderate or severe erythema was not reported for this patch group.

In a similar study, only 2.3% of patients switching from an oral acetylcholinesterase inhibitor to the transdermal rivastigmine patch experienced an application-site skin reaction.^[16] These reactions were classified as mild to moderate, and were not reported to be the reason for discontinuation in any of the patients. Most commonly caused by contact irritation, patients reported mild erythema and pruritus.

Major factors associated with a patient's risk of a reaction to a transdermal patch are sex, age and medical history.^[14] It has been found that

women have a higher tendency towards the development of allergic dermatitis, whereas the evidence is more controversial as to sex associations in irritant dermatitis. Due to the thinner, less elastic and more fragile skin of the elderly, they are more prone to the development of irritant dermatitis; however, they may be at a decreased risk for allergic dermatitis. A past medical history of eczema may also increase a patient's risk of an irritant reaction. Modifiable risk factors include a larger surface area of skin in contact, a longer treatment duration and an increased concentration of allergen in the patch.^[14] Excessive sweat has been found to increase the risk of skin irritation;^[17] however, the IDEAL trial included a number of countries with hot climates where heavy perspiration is expected, and there was no noticeable difference reported.^[7]

Adverse reactions to transdermal patches are often divided into the two following categories: local irritation due to the patch, or an immunological reaction to a component of the patch.^[9] The differentiation between these two conditions can normally be established by the appearance of the lesion (figure 1), and the temporal relationship of the patch application and removal to the onset and offset of the reaction.

The large majority (80%) of skin reactions to medical patches such as the transdermal rivastigmine patch are of an irritant rather than allergic nature.^[17] In most studies, pruritic reactions were labelled as irritant if the faint erythematous, eczematous plaque had precise borders confined to the area of the patch and lacked induration. Allergic reactions tended to be oedematous or vesicular, had the potential to spread beyond the patch site and typically lasted longer than irritant reactions.^[18] Diagnosis of contact dermatitis and differentiation between allergic and irritant dermatitis was based on clinical examination.

3. Clinical Presentation and Diagnosis of Skin Reactions

Irritant contact dermatitis is caused by direct skin injury with or without cutaneous inflammation from contact with the irritating patch.^[19] As expected, contact dermatitis manifests as mild,

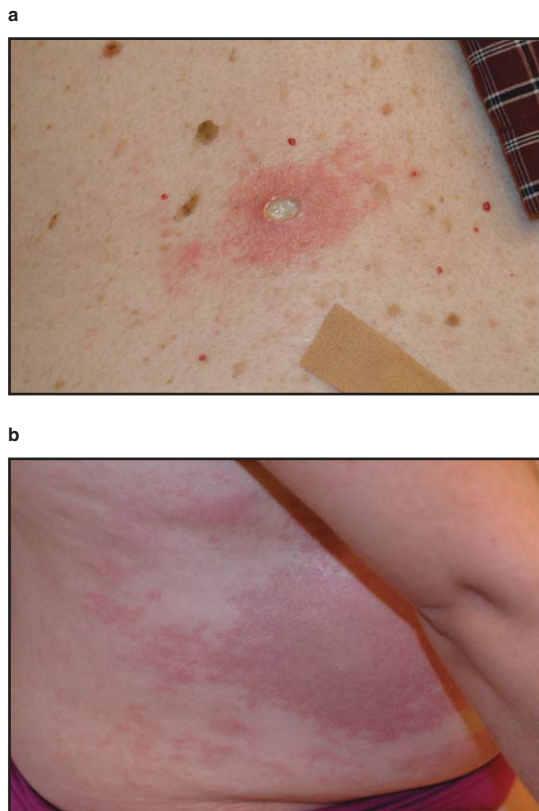


Fig. 1. (a) Acute, allergic contact dermatitis to bacitracin. Bright erythema, vesicles, papules and inflammation are centralized to the peri-wound area with some extension to the periphery. There is relative sparing of the area corresponding to the adhesive in the bandage. (b) Irritant contact dermatitis to phenol. Areas of inflammation are less inflammatory, there are no vesicles and the erythema does not extend at all beyond the areas where the irritant was applied.

well defined erythema. It may be scaly, and patients often report pruritis and mild pain over the area.^[7] The easiest way to confirm the diagnosis is to observe whether the dermatitis disappears upon removal of the irritating substance. If the lesion persists longer than 1 week post-removal of the patch, the clinical suspicion for an allergic reaction increases.

Allergic contact dermatitis is a T-cell-mediated, delayed, type IV hypersensitivity reaction. The relevant allergen with the use of transdermal patches can be the active drug or another inert component of the patch. Allergic dermatitis requires a sensitization phase before an inflammatory

reaction can occur upon subsequent exposure to the patch.^[9] The natural course for allergic dermatitis is complete resolution following removal of the allergen; however, the reaction tends to worsen in the days after the patch is removed, and it may persist for up to 1 month.^[17] Occasionally, re-exposure at a new site may result in a flare of dermatitis at the original site in addition to the new site. Although often difficult to differentiate, several clinical features point to an allergic rather than irritant dermatitis. Features suggestive of an allergic reaction include the presence of vesicles or oedema, extension of the rash beyond the borders of the patch and the lack of a decrease in redness within 48 hours of removal of the patch.^[19,20] Allergic reactions generally last longer than irritant reactions and can persist for months if left untreated.

4. Prevention and Treatment of Irritant Contact Dermatitis

The treatment goal for patients with irritant contact dermatitis is to restore the epidermal barrier and protect it from the original irritating substance. Acutely, cold compresses on the lesion may provide immediate relief of itchy and painful symptoms.^[18] Patients are encouraged to decrease the use of harsh soap, which increases the pH of the skin and removes the natural acidic protection, making the skin more vulnerable to irritation and infection. They should also increase the use of lipid-rich moisturizers.^[18] For acute irritant dermatitis, it has been found that a moisturizing cream containing 5% urea and 5% hydrogenated canola oil applied twice daily for 14 days significantly improved barrier function and skin hydration in an experimentally induced irritant contact dermatitis.^[21] A related study investigated nine different lipid moisturizers and concluded that canola oil was the only moisturizer shown to decrease the irritation of the rash.^[22]

While corticosteroids have been shown to have a beneficial effect in allergic contact dermatitis,^[23] their role in treating irritant contact dermatitis is controversial. Levin et al.^[24] found corticosteroids to be ineffective in treating surfactant-induced irritant dermatitis. Irritant contact dermatitis was induced in healthy volunteers with the applica-

tion of sodium laurilsulfate five times in 24 hours on the hands. Treatment with 1% hydrocortisone or 0.1% betamethasone valerate showed no significant difference from untreated skin. Potent corticosteroids may be required in severe reactions; however, systemic corticosteroids are not helpful and are discouraged due to the adverse effects associated with their use.^[18]

There is inconclusive evidence for the use of barrier creams in preventing irritant contact dermatitis. In a study by Zhai et al.,^[25] a 2% dimethicone skin protectant lotion significantly decreased skin irritation to sodium laurilsulfate-induced irritant contact dermatitis. However, Perrenoud et al.^[26] showed that a barrier cream containing 5% aluminium chlorohydrate as its active ingredient was ineffective in preventing irritant contact dermatitis, and was worse than the vehicle control. Thus, for irritant contact dermatitis the most reliable prevention strategy is avoidance of the irritating substance.^[17]

5. Prevention and Treatment of Allergic Contact Dermatitis

When treating allergic contact dermatitis, oatmeal baths and calamine lotion can provide relief in mild reactions.^[18] A 1- to 2-week course of topical corticosteroids of medium to strong potency is effective in most cases of moderate dermatitis. When more than 10% of the body is covered, treatment with systemic corticosteroids and antihistamines may be required. Prednisone 40 mg daily for 4–6 days, followed by 20 mg daily for 4–6 days is effective and usually well tolerated. With avoidance of the exposure, control of the dermatitis is usually accomplished within 2–4 weeks.^[18] In patients who cannot avoid continued exposure to the allergen, it is possible to treat the dermatitis with a topical calcineurin inhibitor (e.g. pimecrolimus or tacrolimus) or a high-potency topical corticosteroid.^[27] One percent pimecrolimus cream was comparable to 0.1% betamethasone valerate cream in the treatment of nickel-induced allergic dermatitis, and both were more effective than the vehicle.^[28] Continuous application of topical corticosteroids to the same site for longer than 3 weeks should be avoided if possible.^[29]

Research on the prevention of allergic dermatitis is more promising than that of irritant dermatitis. After pre-treating an area of skin for 10–14 days with topical corticosteroids, Langerhans cells decrease significantly or completely disappear.^[30] Sensitizing compounds applied to sites with a decreased local density of Langerhans cells can lead to anergy and eventual tolerance.^[31] In a study by Amkraut et al.,^[27] coadministration of a known sensitizing agent, chlorphenamine, with topical hydrocortisone reduced the incidence of sensitization reactions from 15% to 1%. Thus, it may be possible to prevent or minimize allergic dermatitis by following a pre- and post-treatment corticosteroid regimen.

6. Illustrative Case

A 65-year-old woman presented to our dermatology clinic with intolerance to the rivastigmine patch. She had been tried on this patch and had an excellent response in terms of her Alzheimer's disease symptoms. However, in all sites where the patch was applied she developed circular, red, itchy, swollen, uncomfortable plaques that would last for weeks (figure 2). With rotation of the patch, her upper torso became riddled to the point where she had to discontinue use of the patch. After careful history and examination, a diagnosis of allergic contact dermatitis was made and the patient was prescribed 0.05% betamethasone dipropionate glycol ointment to be applied to the

inflamed areas. This topical therapy, in addition to a rotational schedule developed by the patient's husband and the attending psychiatrist, led to a symptomless tolerance to the patch and the patient experienced a marked therapeutic response to rivastigmine. The steps in this regimen are detailed in figure 3.

7. Practical Considerations for Patch Use and Summary of Recommended Management of Skin Reactions

To minimize the occurrence and severity of all patch-associated skin reactions, regular rotation of the application site is recommended. More specifically, rotating the patch to a new lymph node catchment area may reduce the immunological exposure and prevent or delay a hypersensitivity reaction.^[14] When comparing patch locations, all areas – upper back, chest, abdomen, thigh and upper arm – show similar adhesiveness; however, the greatest medication exposure is achieved when the patch is in contact with the upper back, chest and upper arm. Furthermore, there is a decreased risk of irritation when the patch is placed on one of these locations compared with the upper thigh or abdomen, which increases the patient's risk of developing an erythematous reaction after patch removal.^[32] Placing the patch in a hard-to-reach area, such as the upper back, should be considered when dealing with an uncooperative patient, as this will make it more difficult for the patient to remove the patch.

Also, making sure to not place the patch on the exact same skin location within 12 days of its previous use, moisturizing exposed skin sites and trimming instead of shaving hair at the application site have all been found to minimize the risk of irritation.^[17] Occlusion of skin that has recently been exposed to soap increases the risk of irritant dermatitis, thus it is recommended that patients not apply the patch immediately after cleansing.^[33] Furthermore, patients should not moisturize immediately before application, as this will decrease the sealing of the patch to the skin.^[33] Damage to the stratum corneum can lead to the exposure of deeper layers of skin to the patch, further increasing the patient's risk for an



Fig. 2. Allergic contact dermatitis secondary to a rivastigmine patch. A fading dermatitic reaction is seen overlying the upper left scapula. The rivastigmine patch is in place over the right scapula.

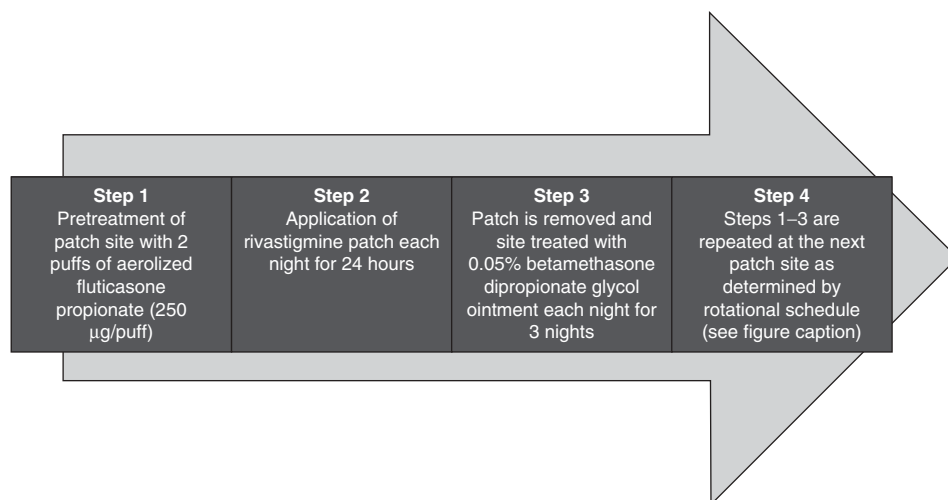


Fig. 3. Management plan for a patient's rivastigmine patch-induced dermatitis. The process that achieved control of this patient's dermatitis is outlined in section 6. After the patch is removed the steps are repeated at the next anatomical site in the rotation (left arm, right arm, left chest, right chest, left upper back, right upper back, left lower back, right lower back). For each anatomical site, a different position within each site is utilized on subsequent rotations (e.g. rotation 1: left arm anterior position; rotation 2: left arm posterior position).

adverse reaction, thus areas with cuts, burns or other damage should be avoided.^[14]

Especially when dealing with elderly patients, who have thinner, more fragile skin, transdermal patches should be removed slowly and carefully to minimize stratum corneum damage, prevent accidental hair removal and prevent erythematous, inflammatory skin responses. Leftover adhesive material can be removed with an oil-based substance, followed by a gentle cleanse with water, to reduce exposure to excess irritants or allergens.^[14] If the patch accidentally falls off or is removed, a new patch should be placed on immediately, and subsequently removed at the original removal time the next day.^[13] Likewise, if application of a patch is missed, a new patch should be applied as soon as it is remembered, regardless of the time of day. Extra patches should not be worn at the same time to make up for a missed dose. While the patch can be applied at any time during the day, it is recommended that patients or caregivers apply the patch at a consistent time each day to improve patient compliance.

As of 31 July 2009, 129 cases of medication errors associated with the Exelon® Patch were reported worldwide, two of which were fatal.^[34] The most frequent cause of overdose was failure

to remove the old patch before applying the new one. Typical symptoms of overdose are similar to the common medication adverse effects, which include nausea, vomiting, diarrhoea, sudden-onset hypertension, hallucinations, sweating, respiratory distress and convulsions.

Patients with a suspected irritant dermatitis, presenting as a pruritic erythematous plaque confined to the borders of the patch, should minimize harsh soap and water use and increase emollient application to the affected areas. If ineffective, topical corticosteroid use may be considered.

Patients with an allergic dermatitis will likely benefit from long-term pre- and post-treatment with topical corticosteroids or topical calcineurin inhibitors. Patients should not apply pre-treatment of corticosteroids to the patch site immediately prior to application as the effect on medication absorption is unknown.^[33] Systemic corticosteroids should be limited to use in patients with more severe dermatitis, at which point a change in Alzheimer's disease treatment should be considered.

8. Conclusions

Alzheimer's disease is a progressive and increasingly common illness. Transdermal delivery

of rivastigmine may increase compliance and efficacy by decreasing the most common adverse effects of nausea and vomiting; however, there is an associated risk of application-site reactions, most commonly contact dermatitis. Rotation of the application site at each new patch application and proper emollient treatment of the exposed sites have been found to minimize irritation. If a site reaction does occur, it is necessary to determine the reaction type and treat the area accordingly. Strategies for coping with both irritant and allergic local reactions are important to ensure that these adverse reactions do not limit a patient's access to this treatment.

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Correspondence: *Jill Greenspoon*, 520 Talbot Street – Unit 412, London, ON, N6A6K4, Canada.
E-mail: jgreenspoon2013@meds.uwo.ca

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