

Allergic contact dermatitis from a clonidine transdermal patch used to treat tic disorders: First pediatric case report and literature review

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Abstract

Background: Recently, clonidine has been increasingly utilized for the treatment of tic disorders in children rather than for hypertension in adults. The transdermal patch is a common route of administration. Allergic contact dermatitis caused by clonidine transdermal patch was reported in adults with hypertension but never in children with tic disorder.

Objective: We report on the first pediatric case developed allergic contact dermatitis within one to two weeks after using clonidine transdermal patch.

Method: Patch test with clonidine and Chinese baseline series including adhesive components (ethyl acrylate, methyl methacrylate, and 2-hydroxyethyl methacrylate) from the adhesive layer of the transdermal patch were performed.

Results: We report the first pediatric case with allergic contact dermatitis due to clonidine transdermal patch confirmed by patch test. She presented with pruritic erythema, blistering, and rupture at the patch site, matching its size and shape. Patch test with clonidine hydrochloride elicited positive reactions (++ to +++), while tests for specific components from the adhesive layer, including ethyl acrylate, methyl methacrylate, and 2-hydroxyethyl methacrylate, were negative, thereby identifying clonidine as the primary allergen.

Conclusion: This case highlights that although clonidine itself has weak sensitizing potential, the transdermal therapeutic system may increase the risk of clonidine-induced sensitization and make it become a potential trigger for allergic contact dermatitis in clonidine transdermal patch users.

Key words: allergic contact dermatitis, case report, clonidine, transdermal patch, patch test

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Background

Clonidine, an alpha 2-adrenergic agonist, indirectly affects central dopaminergic neurons. It alleviates the symptoms of tic disorders (TD) by inhibiting the release of norepinephrine from presynaptic terminals in the locus coeruleus, and therefore is used to treat TD in children.^{1,2} Clonidine is administered by the transdermal patch to treat TD. Here, we reported a child with allergic contact dermatitis (ACD) from clonidine transdermal patch.

Case Report

A 6-year-old girl was prescribed a clonidine transdermal patch on her back to treat TD. The transdermal patch was circular with an area of 1.25 cm² and contained 1 mg of clonidine. The patch was applied to the area below the scapulae on her back and replaced weekly. On the third day of using the fifth patch, obvious pruritus developed

at the application site. After patch removal, regular round erythematous maculopapules were observed locally, with vesicles, erosion and exudation on the surface. In addition, 3 scattered, regular round dark erythematous macules were observed on her back. The parents stated that faint erythema were found at the patch site after previous removals, but they ignored this finding because the girl complained only mild pruritus. According to the similar size and shape between the patch and skin lesions, the provisional diagnosis was ACD from a clonidine transdermal patch. Based on the number of round skin lesions, we speculate that the patient developed ACD as early as during the use of the second patch, specifically between 1 and 2 weeks after patch application. The skin lesions improved on treatment with topical corticosteroids.

Clonidine and transdermal patch materials are both possible contact allergens. To identify the culprit allergen, we performed a patch test with clonidine hydrochloride at 7.6 mg/mL in water and at 10% and 20% in petrolatum on the dorsum of the patient's forearm. Allergens were applied with IQ Chambers™ (Chemotechnique Diagnostics,

Vellinge, Sweden). The results were evaluated according to the European Society of Contact Dermatitis guidelines on Days 2 and 3. On Day 3, clonidine hydrochloride at 0.76% produced a ++ response, and clonidine hydrochloride at 10% and 20% a +++ response, which included erythema, blistering, and extension of erythema beyond the patch test site (**Figure 1**). The Chinese baseline series of patch tests containing ethyl acrylate, methyl methacrylate and 2-hydroxyethyl methacrylate from the adhesive layer were negative in the patient. A patch test with clonidine hydrochloride produced no reaction in three healthy control who had no history of using this drug.

Thus, we inferred clonidine hydrochloride itself as the probable allergen responsible for this patient's ACD and instructed her parents to ensure that the patient avoid using clonidine hydrochloride in the future.

Discussion

Clonidine, chemically named [2-(2,6-dichlorophenyl) imino] imidazolidine with the molecular formula $C_9H_9Cl_2N_3$, is an α_2 -adrenoceptor agonist. It primarily exerts its effects by activating central α_2 -adrenoceptors, inhibiting norepinephrine release, and regulating dopaminergic neuronal activity. Due to its ability to suppress the vasomotor center and peripheral sympathetic nervous function thereby reducing blood pressure, clonidine is used in the treatment of hypertension, but the clinical application of its oral formulation is now rare. The clonidine transdermal patch was approved by the U.S. Food and Drug Administration (FDA) for hypertension treatment in 1984. Given its regulatory effect on dopaminergic neuronal activity to reduce tics, clonidine was further approved by the FDA for the treatment of attention deficit hyperactivity disorder (ADHD) in 2010. In 2011, clonidine was recommended for tic disorders (TD) management in Europa (1), and was recommended for children with TD comorbid with ADHD in 2019 by the American Academy of Neurology.²

The mechanism underlying clonidine's therapeutic effect in TD remains incompletely understood, which may be associated with the following pathways: activating presynaptic α_2 -adrenoceptors in the locus coeruleus to reduce norepinephrine release, or alleviating tics by stimulating γ -aminobutyric acid (GABA) release.³ Additionally, it may directly activate postsynaptic α_2 -adrenoceptors in the hypothalamus and medulla oblongata, excite inhibitory neurons, reduce central sympathetic nerve impulse output, and thereby inhibit peripheral sympathetic nervous activity. α_2 -adrenoceptor agonists can activate α_2A -adrenoceptors (α_2A -AR), improve spatial working memory by inhibiting cyclic adenosine monophosphate (cAMP) production, closing hyperpolarization-activated cyclic nucleotide-gated channels, and enhancing functional connectivity in the prefrontal cortical network.⁴

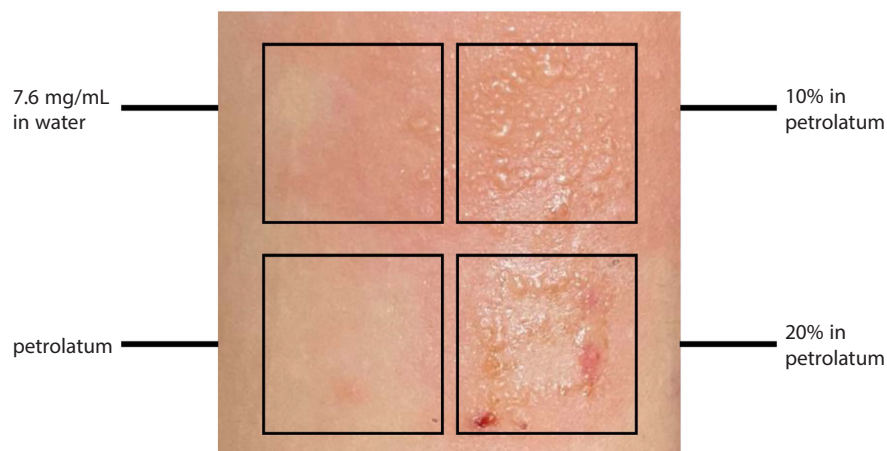


Figure 1. Patch test results with clonidine hydrochloride. Clonidine at 7.6 mg/mL in water showed a ++ reaction and at 10% and 20% in petrolatum showed +++ reactions.

The clonidine transdermal patch is a membrane-controlled transdermal therapeutic system (TTS), composed of a backing liner, a drug reservoir, a release membrane, an adhesive liner, and a protective liner (removed prior to application) (**Figure 2**). The backing layer is a composite film of polyester and polyethylene. It protects and supports the entire formulation and also prevents drug penetration and volatilization. The adhesive layer is an acrylate pressure-sensitive adhesive with good compatibility with clonidine molecules. This can ensure transdermal drug permeability, firmly adhere the patch to the body surface, and exhibit low irritation and sensitization. Clonidine in the drug reservoir layer is continuously released at a constant rate

into the body through the rate-controlling membrane and adhesive layer over 7 days. Steady-state plasma concentrations are achieved 2–3 days after administration, and constant drug release within 7 days. TTS can maintain clonidine plasma concentrations stably within the therapeutic range. Currently, there are three specifications of clonidine transdermal patches for tic disorder treatment: 1.0 mg/patch (1.25 cm²), 1.5 mg/patch (1.88 cm²), and 2.0 mg/patch (2.5 cm²). Through the TTS, the clonidine transdermal patch effectively avoids gastrointestinal drug reactions, reduces administration frequency, and improves patient compliance. To date, it has been used in the treatment of pediatric TD for more than a decade.

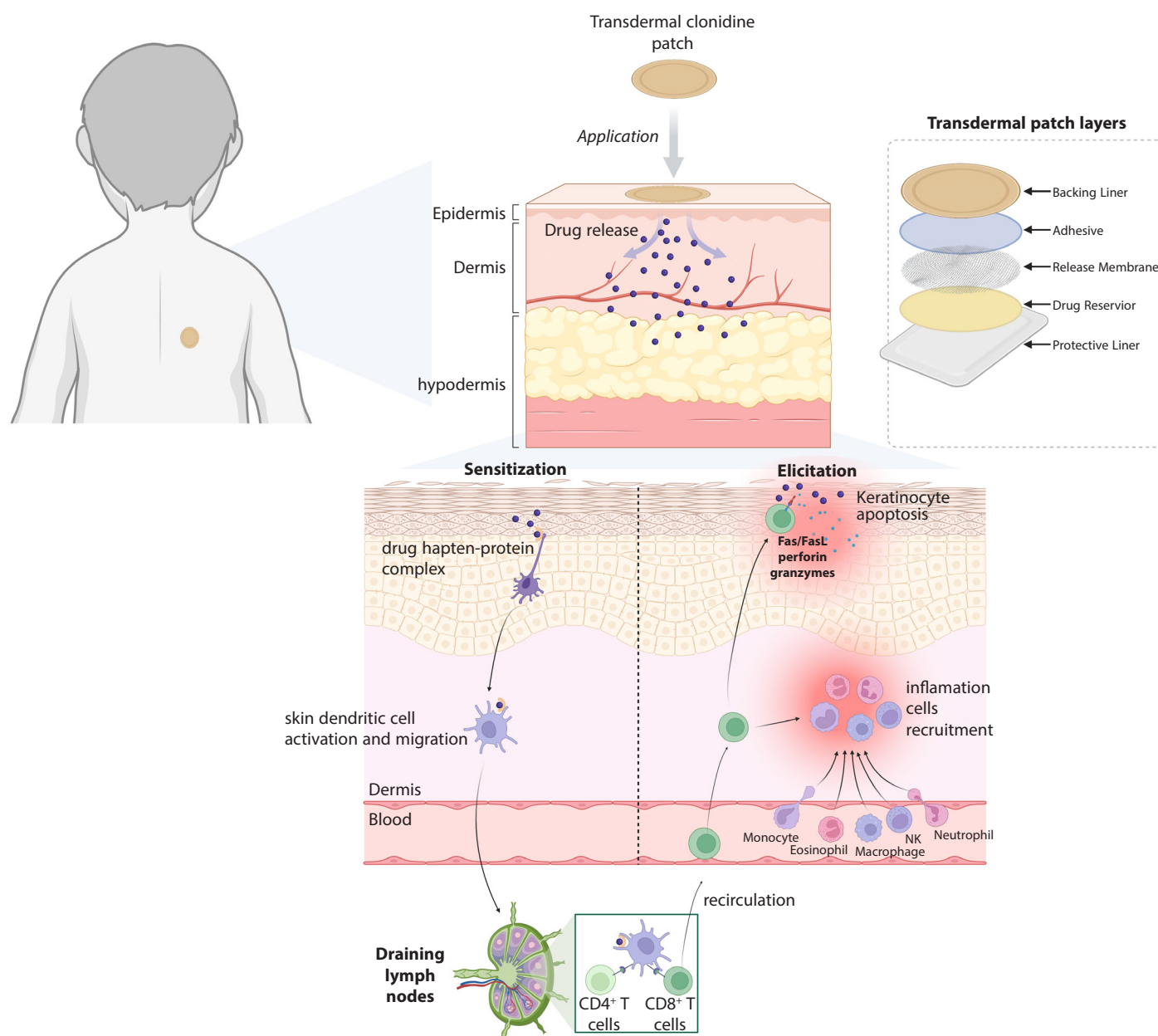


Figure 2. Schematic diagram of clonidine transdermal patch action and induction of allergic contact dermatitis. The transdermal therapeutic system (TTS) releases clonidine, which penetrates the skin and forms hapten-self-protein complexes. These complexes are presented by antigen presenting cell that migrate to regional lymph nodes to activate T cells. Upon re-exposure to clonidine, antigen-specific effector T cells migrate to the skin, kill hapten-bearing keratinocytes and also promote inflammatory cells recruitment.

Skin reactions are common adverse effects of clonidine transdermal patches, mainly including skin irritation and ACD.⁵⁻⁷ The incidence of skin reactions varies significantly among different studies: most data are derived from clinical studies on clonidine transdermal for hypertension conducted in the 1980s to 1990s, with an incidence ranging from 9.4% to 64%, mainly presenting as local pruritus and erythema at the application site.⁵ In contrast, the incidence of skin reactions in patients with TD is significantly lower, only 0.92% to 8.93%.^{8,9} A total of 6 studies on ACD induced by clonidine transdermal patches were retrieved,¹⁰⁻¹⁵ and detailed information is shown in **Table 1**.

The pathogenesis of ACD belongs to type IV hypersensitivity reaction, which is mainly mediated by T cells and divided into two phases: sensitization and elicitation (**Figure 2**).¹⁶ TTS is prone to inducing local ACD by occluding, continuously irritating, and repeatedly exposing the same skin site to potential allergens. The drug component was continuously and stably released by TTS and penetrate the skin and bind to self-proteins to form hapten-self-protein complexes. These complexes are captured and presented by Langerhans cells and dermal dendritic cells, which then migrate to regional lymph nodes to initiate the activation and proliferation of T cells. When re-exposed to the same drug, antigen specific effector T cells and memory T cells migrate directionally to the skin target sites and specifically kill keratinocytes carrying drug haptens on their surfaces.

Due to the long-term persistence of memory T cells in skin tissues, the cutaneous inflammatory response may show a progressive aggravation trend upon repeated exposure to the same drug.

Sensitization may develop from the active pharmaceutical agent, adhesive, or other excipients in the TTS. Clonidine itself has weak sensitizing potential, but the TTS can enhance its sensitizing effect.¹³ Previous literature has confirmed that clonidine itself is the main allergen in the clonidine transdermal patch, while patch tests for other inactive pharmaceutical components in the TTS (such as polyisobutylene) show fewer positive reactions.¹¹ Regarding the culprit allergen, patch testing in this pediatric patient showed a positive reaction to clonidine, while the adhesive components (ethyl acrylate, methyl methacrylate, and 2-hydroxyethyl methacrylate) were all negative. This confirms that the ACD was triggered by clonidine itself rather than the adhesive materials. In terms of demographics, previous reports of ACD induced by clonidine patches were exclusively limited to adult patients, largely because these patches were historically used to treat hypertension.¹⁰⁻¹⁵ However, since their approval for ADHD and TD in children starting 2010, the pediatric user base has grown. As the first reported pediatric case of TD-related ACD from a clonidine patch, this case underscores the need for clinical vigilance in the pediatric population. ACD induced by clonidine transdermal patches typically occurs 3 to 94 weeks

Table 1. Literature review of allergic contact dermatitis caused by clonidine transdermal patch.

Author (Year)	case number	underlying disease	Time to ACD Onset (weeks)	Incidence of ACD % (n)	ACD Manifestations	Diagnostic Method	Identified Allergen
Boekhorst JC (1983) ¹	21	hypertension	≤4	NA	Local erythema, pruritus*	NA	NA
			17	4.7% (1)	Local erythema, infiltration, pruritus	patch test	clonidine TTS
			24	4.7% (1)	Local erythema, infiltration, pruritus, and systemic reaction occurred after 28 weeks	patch test	clonidine TTS
			23	4.7% (1)	Local erythema, infiltration, pruritus	patch test	clonidine TTS
Groth H (1984) ²	32	hypertension	≥4	47% (15)	pruritus, erythema, vesiculation, and/or infiltration	patch test in 8 patients	Clonidine (7 cases); Polyisobutylene (1 case)
Maibach H (1985) ³	92	healthy people	3	4.3% (4)	Local erythema, pruritus	patch test	clonidine
Grattan CE (1985) ⁴	1	hypertension	12	NA	local eczema	patch test	clonidine
Corazza M (1995) ⁵	1	hypertension	4	NA	local pruritus, erythema, vesiculation	patch test	clonidine TTS (Adesipress TTS-2)
Marchetti M (2025) ⁶	1	hypertension	94	NA	local itching, erythematous-desquamative plaques	patch test	clonidine
Present study (2026)	1	tic disorder	1 to 2	NA	Local erythema, pruritus	patch test	clonidine

after the initiation of medication, mainly characterized by local pruritus, erythema, and vesicles at the application site.¹⁰⁻¹⁵ Notably, the onset of ACD in our case occurred between one and two weeks, which is significantly shorter than the 3 to 94 weeks typically reported in adults. The observation that children develop ACD significantly sooner than adults may be attributed to several age-specific physiological factors. It is hypothesized that the thinner stratum corneum and higher body surface area-to-weight ratio in children could lead to a more rapid percutaneous absorption. Additionally, high skin hydration, further increased by the occlusive nature of the patch, likely compromises barrier integrity and facilitates hapten-protein conjugation, thereby hastening the immune response. Previously published data reported that the concentration of clonidine in patch tests varies, being 1%, 3%, or 9% clonidine in petrolatum.^{12,13} We prepared three types of patch preparation, they were 10% and 20% clonidine in petrolatum, and an aqueous solution based on solubility. Patch test with clonidine resulted in ++ to +++ reactions. Based on the patch test results of our patient and previously reported data, it is suggested that a concentration of 10% clonidine in petrolatum can effectively elicit a delayed hypersensitivity reaction while minimizing the risk of severe irritant responses.

Clonidine TTS was initially for treating hypertension and was reported to induce localized allergic contact dermatitis in adults with hypertension. With its recent application in treating TD in children, there have been no ACD incidents in this new demographic. We describe a pediatric case experienced localized ACD roughly within two weeks post-initiation of clonidine transdermal patch therapy for TD, drawing attention to the possible side effects of this drug for doctors.

Ethics approval

The ethics approval has been obtained from the ethics committee of Peking Union Medical College Hospital (I-25PJ3136).

Informed Consent

Informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Conflict of interest

All the authors have no conflict of interest to disclosure.

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Authors' contribution

- Yingyang Xu performed the patch tests, analyzed the results, and drafted the article.
- Yi Ru prepared and performed the patch tests.
- Kai Guan acquired and diagnosed the case, reviewed the article, and gave final approval of the version to be published.

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