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Article type : Letter to Editor

Letter to the Editor JEADV

Title : A case of delayed antihistamine cutaneous drug eruption and piperidine derivative cross- reaction

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Acknowledgement :

The patient in this manuscript have given written informed consent to the publication of their case detail.

Conflict of interest :

No author has any conflict of interest concerning this clinical case and during the time of its realization, concerning it.

One of the author presents consulting fees during past 36 months outside of this clinical case.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JDV.17511](#)

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Dear Editor

Antihistamines are commonly used medications for the treatment of allergic diseases or chronic spontaneous urticaria. They are usually well tolerated and effective. Antihistamines are classified into six chemical groups : piperazines, piperidines, phenothiazines, ethanolamines, ethylenediamines and alkylamines. Among antihistamines, piperazines are the most frequent inducers of hypersensitivity.¹ Immediate hypersensitivity as cases of urticaria or anaphylaxis are usually reported but delayed reactions are also possible.

We report a case of a 51-year-old man without medical history who was treated with antihistamines for chronic spontaneous urticaria. According to international recommendations he received successively, desloratadine, a piperidine derivative, 4 tablets per day, which was not effective, then levocetirizine, piperazine derivative, 4 tablets per day. Because of asthenia, ebastine, a second piperidine derivative, 4 tablets per day was introduced. Four days after the introduction of ebastine, he developed maculopapular exanthema initially with a flexural disposition secondarily extended to the trunk. There was no adenopathy, fever, mucosal involvement or biological abnormalities (Fig.1). Ebastine was stopped and the symptoms disappeared in a few days. Skin biopsy was compatible with a drug-induced mechanism revealing spongiosis and rare keratinocytes necroses. Levocetirizine was re-introduced and well tolerated. We concluded at a delayed hypersensitivity due to ebastine. Patch tests were performed with piperidines (fexofenadine, loratadine, desloratadine, ebastine) and piperazines (hydroxyzine, cetirizine) in 30% petrolatum. After 72 hours, both ebastine and desloratadine patches were positive based on ICDRG criteria (Fig.1).² Skin biopsies were performed on both positive patch areas and confirmed histopathological aspects of contact dermatitis. We report what we believe to be the first case of delayed hypersensitivity to ebastine with cross reactivity within the piperidine chemical class.

The most common adverse effects of antihistamines are due to their own binding activities to H1 receptors, muscarinic receptors, serotonin receptors and cardiac ion currents and may cause sedation, increase of appetite, buccal dryness, urinary retention, tachycardia, hypotension, dizziness, prolonged QT interval and hypersensitivity. Like other treatments, they can induce immediate or delayed hypersensitivity reaction. According to the French pharmacovigilance database, 39 cutaneous rashes are indexed with ebastine among which ebastine was the only suspected drug in 22 cases. Kurihara et al³ described the clinical features of 138 antihistamine-induced cutaneous reactions, both immediate and delayed. The most frequent were urticaria, followed by fixed drug eruption (FDE), anaphylaxis, maculopapular rash, eczematiform dermatitis, acute generalized exanthematous

pustulosis (AGEP), photosensitive dermatitis and toxic epidermic necrolysis. Within delayed reactions, the sensitivity of patch test was estimated around 80% for fixed drug eruption and acute generalized exanthematous pustulosis but only around 38% for maculopapular rash. FDE are commonly described and all were induced by piperazines. Cases of AGEP have been described with hydroxyzine⁹ a piperazine derivative, with positive patch test. Only a few cases of antihistamine-induced delayed maculopapular eruptions have been reported (Fig 2)¹⁴⁵⁶⁷⁸. Concerning cross-reactivity, Kim et al¹⁰ reported a FDE due to levocetirizine with positive patch tests for several piperazines: levocetirizine, cetirizine and hydroxyzine. An oral challenge to fexofenadine, a piperidine derivative was well tolerated. Lew et al¹ described a delayed maculopapular eruption due to hydroxyzine confirmed with positive patch tests to hydroxyzine and cetirizine, both piperazine derivatives. We report what we believe to be the first case of delayed maculopapular exanthema due to a piperidine derivative, with positive patch test and cross-reaction with other antihistamines from the same chemical group.

Acknowledgement :

The patient in this manuscript have given written informed consent to the publication of their case detail.

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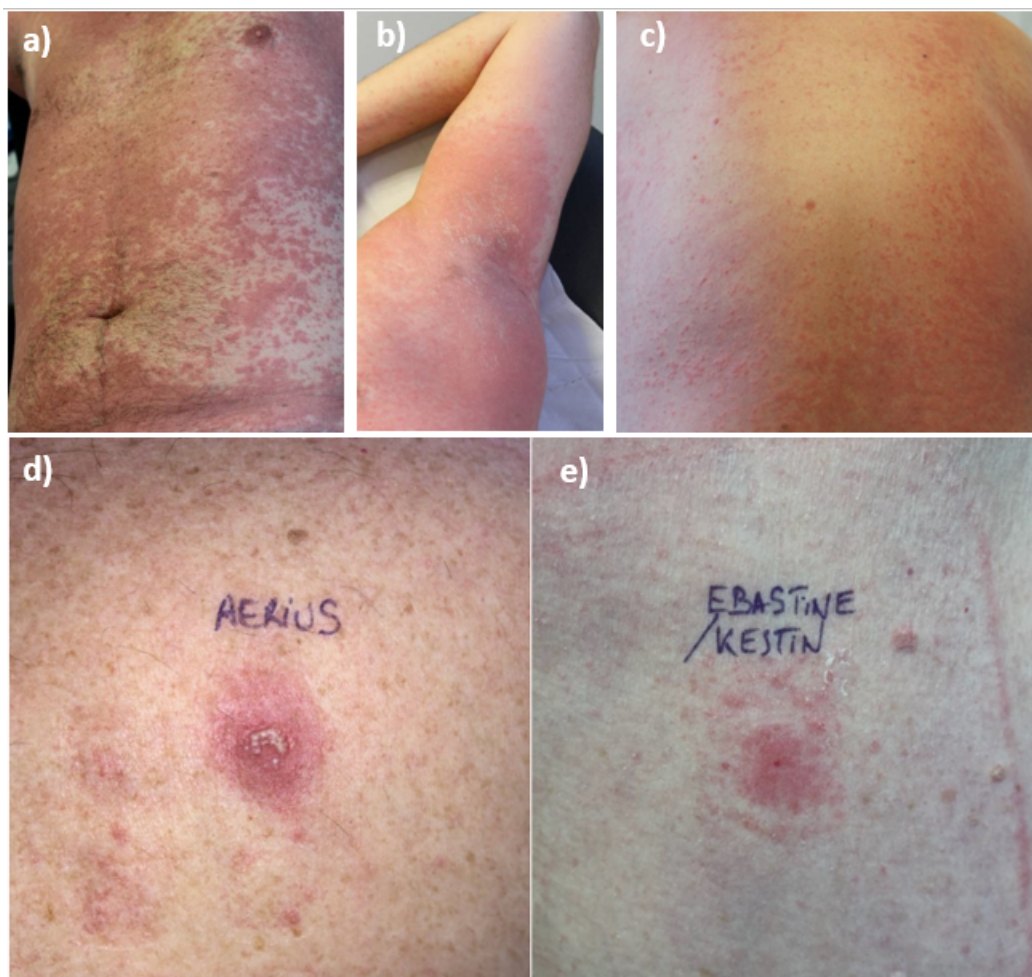


Figure 1 Exploration of maculopapular exanthema with trunk involvement (a), with flexural disposition (b) and on the patient's back (c), with positive patch test to desloratadine/Aerius® (d) and ebastine/Kestin®.

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Figure 2 Review of antihistamines' toxidermia (except fixed drug eruption and pustular-type drug-induced).

References	patients Age/sex	Clinical aspect	Drug	Oral provocation test	Patch test	Prick test
Michel (1997) ⁴	F/65 y	Maculopapular eruption	Hydroxyzine	+	+	-
	F/20 y	Maculopapular eruption	Hydroxyzine	+	+	-
	F/35 y	Maculopapular eruption	Hydroxyzine	+	+	-
Ash (1997) ⁵	F/48 y	Maculopapular eruption	Hydroxyzine	+	+	ND
Stingeni (1997) ⁶	F/70 y	Maculopapular eruption	Cetirizine	+	+	-
Benhayoun (2013) ⁷	M/51 y	Maculopapular eruption	Hydroxyzine	ND	+	NC
Vinas (2014) ⁸	F/70 y	Maculopapular eruption	Cetirizine	-	+**	ND
Lagassy (2019)	M/51 y	Maculopapular eruption	Ebastine	+ *	+ ***	-

F : Female; M : male.

NC : not communicated; ND : not done.

* : test performed with LEVOCETIRIZINE.

** : patch test positive to HYDROXYZINE.

*** : patch test positive to EBASTINE and DESLORATADINE.

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