

Ephedrine-induced erythrodermia: Clinical diagnostic procedure and cross-sensitivity

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Ephedrine hydrochloride (HCl) injection is part of the World Health Organization model list of essentials for use in anaesthesia to treat hypotension induced by some anaesthetics. Ephedrine hypersensitivity reactions have very rarely been described, and those cases caused by analogues are most often related to contact dermatitis as the clinical presentation. However, cases of systemic reactions have been published (Table S1). We present here a case of ephedrine-induced erythrodermia, with cross-sensitivity to phenylephrine and epinephrine/adrenaline, but not to pseudoephedrine.

CASE REPORT

A non-atopic 78-year-old man underwent colonoscopy for an intestinal polyp biopsy under general anaesthesia, for which he received fentanyl, sufentanyl, cisatracurium, and amoxicillin/clavulanic acid. Ephedrine was injected during the intervention, owing to a circulatory collapse secondary to the pharmacological effect of the neuromuscular relaxant agent. Within 48 hours after the procedure, the patient presented with a pruritic maculopapular eruption on the trunk, back, and upper limbs, with no associated systemic symptoms. The lesions progressed to erythrodermia with desquamation; however, laboratory test findings remained within normal limits. After treatment with systemic corticosteroids and H1 antihistamines, the patient recovered within 14 days and was advised to undergo further investigation. On the basis of the patient's history, ephedrine and amoxicillin/clavulanic acid were considered to be the main suspect drugs. Hence, skin prick and intradermal tests with penicillins and a single blind oral provocation test with amoxicillin/clavulanic acid were performed, following the European Network on Drug Allergy guidelines,^{1,2} with negative results.

Patch tests gave positive reactions to ephedrine 10% both in aq. and pet. on day (D) 3 (++) and a positive reaction to ephedrine

1% aq. (+) on D2. Moreover, patch tests performed to evaluate cross-sensitivity to epinephrine/adrenaline, motivated by the relevance for emergency treatment, gave positive reactions (++) on D3 to epinephrine/adrenaline (1% and 5%) both in pet. and in aq. Six healthy controls had negative patch test results with epinephrine/adrenaline 10%, both in pet. and in aq. In addition, cross-sensitivity was also assessed by the use of patch tests with phenylephrine (1%), oxymethazoline (10%) and pseudoephedrine (10%, 20%, and 30%), all both in aq. and in pet., with a positive reaction to phenylephrine, but negative results with the other analogues.

DISCUSSION

Most cases of generalized reactions to sympathomimetic drugs, both immediate and non-immediate reactions, are related to systemic exposure to pseudoephedrine. Ephedrine-induced sensitivity has been previously reported,^{3,4} but only 1 case of a generalized non-immediate reaction to synthetic epinephrine/adrenaline has been reported over the last 2 decades (1997-2017) (Table S1). If such hypersensitivity is suspected, appropriate diagnostic investigation is crucial. Once the diagnosis is confirmed, finding alternative sympathomimetic drugs is essential, for the following reasons: (1) the importance of this medication for possible future needs; and (2) the avoidance of inadvertent re-exposure to formulations containing sympathomimetic drugs.

Although a written recommendation has been provided to the patient in case epinephrine injection is needed in the future, we advised that epinephrine/adrenaline should not be withheld in acute life-threatening situations, such as anaphylaxis, also considering that the positive predictive value of a positive patch test reaction to epinephrine is unknown.

Patch testing with drugs can confirm in vivo T lymphocyte-mediated allergic diseases and/or sensitization in subjects with non-

immediate reactions to drugs, by reproducing a local allergic reaction on a small area. The specific mechanism of non-immediate reactions to epinephrine remains unknown. However, previous publications have shown that patch testing can provide the diagnosis of T lymphocyte-mediated hypersensitivity caused by this pharmacological group as well as support cross-sensitivity evidence.^{3–20} Pharmacological interaction has also been hypothesized in non-immediate reactions to drugs.²¹ In recent years, evidence has become stronger that not all drugs need to bind covalently to the major histocompatibility complex (MHC)-peptide complex in order to trigger an immune response. According to the pharmacological interaction concept, some drugs may bind directly and reversibly to immune receptors such as MHC or the T cell receptor, thereby stimulating the cells in a similar way to pharmacological activation of other receptors.²¹

The drugs tested belong to the phenylamine family, which comprises 2 main groups of drugs: phenylpropanolamine-derived (ephedrine, pseudoephedrine, and norephedrine) and phenylethanolamine-derived (phenylephrine and epinephrine/adrenaline).⁵ The very close chemical similarity of these drugs could explain potential cross-reactions among them. Although some authors have observed cross-reactions between ephedrine and pseudoephedrine,^{6,7} others have not.⁴ It is also known that the molecular structure of agents of the same group is a key factor in allowing a chemical hapten to be recognized by the immune system, due to the hierarchical clustering in function of the electrostatic and steric fields of these molecules.⁸ For example ephedrine and pseudoephedrine do not usually cross-react. The presented data suggest that ephedrine was most likely the culprit drug, with cross-sensitivity to frequently used analogues.

Published data show the use of different concentrations for the performance of patch tests, generally with in-house preparations. We also applied an in-house preparation in our case, as a standardized hapten formulation for patch testing for sympathomimetic agents is not available in France. The variability in performing drug patch tests due to lack of appropriate number of cases and based on own methods (concentration and vehicle) and validation (different number of controls) may hamper comparability between published cases.

Although the sympathomimetic drugs can rarely induce exanthematous drug reactions, this case of ephedrine-induced erythrodermia supports the need to investigate these drugs as a cause of generalized non-immediate reactions.

Conflict of interest

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table 1: Summary of cases of generalized reactions non-immediate induced by sympathomimetic drugs published in the last 2 decades (1997-2017) and documented by *in vivo* diagnostic methods.

Reference	Gender (F/M), age (y)	Country	Culprit drug	Phenotype	Skin test	Negative healthy controls for skin test (N)	Drug provocation test	Cross-sensitivity
Nagge et al, (2005) (9)	F, 57y	Canada	Pseudoephedrine	TEN	PT Pseudoephedrine (3% pet.) +	3	Inadvertent re-exposure (cough syrup) +	ND
Gonzalo-Garijo et al. (2002) (10)	F, 18y	Spain	Pseudoephedrine	Erythrodermia	PT Pseudoephedrine and phenylephrine (1,5,10%, pet.) +	ND	Inadvertent re-exposure (cough tablet) +	+ (Phenylephrine)
Mayo-Pampín et al. (2006) (11)	M, 40 y	Spain	Pseudoephedrine	Acute Generalized Exanthematous Pustulosis	PT (2.5, 5% pet.) pseudoephedrine +	ND	ND	ND
Millard et al. (2003) (12)	F, 44y	United Kingdom	Pseudoephedrine	Erythrodermia	PT (20% pet.) pseudoephedrine +	15	ND	ND
Moreno-Escobosa et al. (2002) (13)	F, 70y	Spain	Pseudoephedrine	Dermatitis	PT: pseudoephedrine, ephedrine (10% pet., aq.)++ Phenylephrine (10%pet, aq.) ++ Epinephrine (1:1000) -	10	ND	Phenylephedrine, ephedrine
Diaz-Jara et al. (2002) (14)	F, 71y	Spain	Pseudoephedrine	Pigmented purpuric dermatosis	PT pseudoephedrine (10% and 20% in DMSO) ++ in 12h Skin biopsy: extravasated erythrocytes, perivascular inflammation with lymphocytes	ND	DPT: 15mg pseudoephedrine: + at 4h	ND
Yokose C et al. (2013) (15)	F, 18y	Japan	Methylephedrine (anti-cough)	Maculopapular eruption	PT anti-cough, toclase, kaigen: all negative	ND	anti-cough (1/10,1/5,1/2,1) : + after 2 h at dose 1, toclase (1/10,1/5, 1/2, 1) : negative Kaigen (1/10, 1/5, 1/2, 1) : negative, acetaminophen : negative	ND

Padial MA et al. (2004) (16)	F, 42y	Spain	Pseudoephedrine	Generalized exanthematous pustulosis	- skin biopsy : spongiform superficial pustules and papillary oedema with focal necrosis of keratinocytes - PT ephedrine, phenylephedrine, epinephrine, norepinephrine (20% and 50% pet.) : positive for ephedrine, negative for others	4 (2 atopic patients and 2 healthy controls)	DPT with phenylephedrine (7.5mg) and ephedrine (5mg): negative Subcutaneous ephedrine (1/1000 - 0.3ml): negative	None
Sanchez-Morillas L. et al. (2003) (17)	F, 20y	Spain	Pseudoephedrine	Symmetrical drug related intertriginous and flexural exanthema	- PT atiramin, iniston, pseudoephedrine ephedrine, epinephrine(1%), terbutaline, salbutamol (5mg/ml) on both normal and affected skin : both positive for iniston, both negative for atiramin, ephedrine, epinephrine and pseudoephedrine - skin biopsy (from positive patch with iniston): hyperkerotosis, dermal fibrosis, lymphocystic infiltrate	5	- DPT with salbutamol and terbutaline : negative - subcutaneous epinephrine negative	No
Assier-Bonnet H et al. (2002) (18)	M, 68y	France	Pseudoephedrine	Exanthematous pustulosis	- PT: pseudoephedrine (10%) ++	ND	ND	ND
	F, 51y		Pseudoephedrine	Generalized papulovesicular eruption with facial oedema and mucosal erosions	- PT sirup ++ and pseudoephedrine (10% pet.) ++	ND	ND	ND
Ben Salem C et al. (2008) (19)	F, 31y	Tunisia	Pseudoephedrine	Acute generalized exanthematous pustulosis	ND Skin biopsy: Subcorneal spongiform pustule with neutrophils. Inset with necrolytic keratinocytes and eosinophils.	ND	DPT with paracetamol: negative (suspected drugs: paracetamol and pseudoephedrine)	ND

Añibarro B et al. (1998) (20)	F, 19y	Spain	Pseudoephedrine	Nonpigmented fixed exanthema	- PT phenylephrine (1% and 10% pet.): slight erythema at 96h	ND	DPT with Iniston (pseudoephedrine 60mg + triprolidine 2.5mg): positive	No
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F: female, M: male, y: years, PT: Skin patch test, DPT: oral provocation test, ND: not done; TEN = Toxic Epidermal Dermatitis, IDT= intradermal skin test