

ALLERGYNet

ALLERGY 1997; 52: 229-239

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• ISSN 0105-4538

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Nonpigmenting fixed exanthema from ephedrine and pseudoephedrine

THE NONPIGMENTING form of the fixed drug eruption has become a recognizable clinical entity. The epidermis is not disturbed, and thus no pigmentation occurs. On the other hand, skin reactions to pseudoephedrine and ephedrine are apparently rare, and very few cases of nonpigmenting fixed drug eruption have been reported (1-3). Cross-reactivity does not always exist between sympathomimetic drugs (SD); thus, they should not be routinely prohibited in cases of hypersensitivity.

In this report, we describe a female patient who presented nonpigmenting fixed exanthema after administration of pseudoephedrine and ephedrine. Other SD, on parenteral or oral challenge, caused no positive reaction.

■ The patient was an 18-year-old woman with no medical history of interest. Five months before coming to our department, she had had an upper airway infection, for which her physician prescribed Fluidin codeina (ephedrine hydrochloride 5 mg, codeine 10 mg, guaifenesin 100 mg). Having taken the first dose, she presented, after a latency period of 7-8 h, tender, erythematous plaques on the palms, abdomen, and groin areas, measuring approximately 8 cm in diameter. The drug was discontinued, and the eruption resolved without pigmentary changes. Four months later, an identical sequence of events occurred with one capsule of Narine (loratadine 5 mg, pseudoephedrine 60 mg).

Patch tests were performed with the following SD: ephedrine, pseudoephedrine, phenylephrine, epinephrine, phenylpropanolamine (1%, 5%, 10% pt.), and terbutaline 1% aq. No reactions were observed.

The patient was then challenged orally with 50 mg of pseudoephedrine. Within 8 h, the same erythematous eruption appeared at exactly the same sites as her two previous attacks. The inflammatory skin involved spontaneously within a week without residual pigmentation. An oral challenge with 5 mg of ephedrine was also followed by similar lesions. Oral challenges with phenylephrine (7.5 mg), terbutaline (2.5 mg), salbutamol (2 mg), and phenyl-

propanolamine (30 mg) were negative. She was also tested with subcutaneous epinephrine 1/1000 (0.3 ml), with negative results.

■ SD have been proved to cause various skin lesions (1, 4), but the onset of nonpigmenting fixed exanthema is exceptional. Other drugs causing this reaction pattern (3) include piroxicam, diflunisal, thiopental, iohalamate, and arspenamine. The dermis, rather than the epidermis, is the primary site of the drug sensitivity response in this dermatitis (2).

In this patient, specific, symmetric areas of the skin were sensitized and responsive to pseudoephedrine and ephedrine, which caused a nonpigmenting fixed eruption. It is difficult to clarify the mechanism, but negative patch results do not suggest a type IV reaction. The very similar structures of ephedrine and pseudoephedrine (pseudoephedrine is an isomeric form of ephedrine) could explain potential cross-reactions between these two drugs. Other SD differ much more in molecular structure, and no cross-reaction has been observed with provocation tests. Besides, controlled challenge seems to be the only way to determine the nature of the eruption and to demonstrate cross-reactivity between SD. Patch tests have been inconclusive for us as well as for other researchers (5).

Pseudoephedrine and ephedrine are widely found in remedies for the common cold (26 different formulations in Spain). For this reason, close attention must be paid to their presence in any patient with recurring eruption.

Key words: ephedrine; fixed eruption; pseudoephedrine; sympathomimetic drugs.

J. C. GARCÍA ORTIZ*, M. TERRON, J. BELLIDO
*Hospital Los Montalvos
Servicio de Alergia
37192-Salamanca
Spain
Fax: 23-330165

Accepted for publication 2 November 1996

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ALLERGY 1997;52:229-230

This case of drug reaction did not show any cross-sensitivity to other sympathomimetic drugs.

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Anaphylaxis due to a red harvest ant bite

HYMENOPTERA sting anaphylaxis, a common disorder, is mainly caused in Europe by honeybees (*Apis mellifera*) and wasps (*Vespa* and *Polistes*). In South America and increasingly also in the USA, stings and bites of the fire ant (*Solenopsis invicta*) are becoming an endemic problem (1, 2). These insects attack by biting to attach themselves and then inserting their sting, which contains the venom. Allergic reactions to other stinging ants have also been described. Thus, systemic reactions to stings of the Samsun ant (3) in Saudi Arabia and the jumper and bulldog ants (4) in Australia have been reported. Single cases of anaphylaxis to other ants such as the Ponerinae subfamily (5) have been noted.

We report here an unusual case of severe anaphylactic reaction to a bite of the red harvest ant (RHA) (*Formica rufa*), a widespread species in central Europe.

A 12-year-old boy with known hay fever suffered an ant bite during a forest walk in September.

An unusual case of severe reaction to the bite of an ant common in Europe.

Minutes after the bite, facial flushing, urticarial exanthema, wheezing, and severe dyspnea occurred, requiring treatment with bronchodilators and corticosteroids in an emergency unit.

The boy's mother killed and kept the biting ant, which was identified later as an RHA by a university entomologist. Previously, the boy had tolerated stings of other Hymenoptera such as bees and wasps without allergic reaction.

An allergologic investigation was performed 6 months later. Skin prick tests with a sterile whole-body extract of RHA produced a large wheal and flare reaction in the patient, but were negative in 10 healthy volunteers. For measurement of specific

IgE against RHA, an extract (1/10 w/v) of this ant was coupled to activated disks (5 µl/disk) and incubated with the patient's serum. The patient's serum was clearly positive (1.8 U/ml), while controls with normal and also with high IgE serum gave a negative result. However, a serum positive for the imported fire ant also gave a positive result (1.7 U/ml) with the RHA disks. An immunoblot with the patient's serum and a positive control to imported fire ant (RAST value 2.5 kU/l) detected some common allergens, but mostly there was a clear difference between the two ants. Furthermore, significant amounts of specific IgE against fire ant, honeybee, and wasp were detected in the patient. These findings suggest possible cross-reactivity between the whole-body extract of the European RHA and the venom of this stinging species of Hymenoptera.

The clinical history, the positive specific skin prick test, and the presence of IgE antibodies left no doubt of an anaphylactic reaction to an RHA bite. This evidence also excluded a purely toxic reaction induced by formic acid, the main component of RHA venom.

As far as we know, this is the first reported case in the literature of a well-documented anaphylactic reaction to an RHA bite. RHA venom has not been clearly identified until now. The most important components besides formic acid are protein alkaloids such as dialkylpiperidin, but also enzymes such as hyaluronidase have been found. As the child described here also showed specific IgE to honeybee and wasp, a cross-reaction with some of the common components in these venoms cannot be excluded. Furthermore, the RHA whole-body extract used could contain other cross-reacting proteins. The pre-existing hay fever may have aggravated the anaphylactic reaction in our patient. One study of asthmatic children has found prevalences of specific IgE to common outdoor insects (such as moth, cricket, grasshopper, housefly, and ant) (6). For lack of other sera, further *in vitro* studies of cross-reactivity to define the possible cross-reactivity of the RHA whole-body extract with the venom of fire ant, honeybee, wasp, and phospholipase A could not be performed.

Although RHA bites happen quite often, especially to children, anaphylactic reactions are extremely rare and possibly of clinical importance only in predisposed children. Nevertheless, the case presented here suggests that such a severe, anaphylactic reaction could occur also to common ant bites. Other, similar cases should be investigated to determine the possible cross-reactivity with other Hymenoptera species, because this could have important consequences for patients allergic to the stings of common insects.

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