Anaphylactic Shock to a DEET-Containing Insect Repellent

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Over recent decades, the greater consciousness of a large number of insect-borne diseases (such as malaria, dengue hemorrhagic fever, and West Nile virus) has generated a rapidly growing number of insect repellent applications in attempts to prevent transmission. A reliable option is N-N-diethyl-3-methylbenzamide, otherwise known as N,N-diethyl-meta-toluamide, diethyltoluamide or DEET [1]. DEET was originally patented in 1946 by the US Army for military use in insect-infested areas and subsequently registered in 1957 for use by the general public. Due to its properties, DEET is considered the best protective solution against arthropod-carried diseases and is the major active ingredient in most topical insect repellent solutions [2].

Despite the frequent use of DEET as an insect repellent, very few cases of contact urticaria [3-7] or urticaria [8] caused by DEET have been reported, and to our knowledge, only one previous case of anaphylaxis caused by DEET was published many years ago [9]. We report a case of anaphylactic shock due to the application of an insect “DEET-repellent solution” with a positive allergologic study.

A 28-year-old woman, with a previous history of allergic rhinoconjunctivitis and asthma with sensitization to pollens, experienced tingling of lips after airborne indirect contact of an insect repellent solution called Medcell® (water, diethyoluamide, ethythexylmethoxycinnamate, ethylthexyl salicylate, methylene bis-benzotriazolyl, tetramethylbutyphenol, mineral oil, isopropyl myristate, cetyl alcohol, glyceryl stearate/PEG-100 stearate, cetyl

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acetate/acetylated lanolin alcohol, isopropyl palmitate, methylparaben, fragrance of benzyl benzoate and coumarin, triethanolamine, propylparaben, carbomerl T). Just a few minutes later, the patient applied the same insect repellent Medcell® on her legs. Immediately, she experienced edema in lips, dyspnea, dysphagia, generalized rash, and dizziness. In the Emergency Department, tachycardia, tachypnea, and blood pressure of 90/40 mm Hg were detected. She was treated with intravenous hydrocortisone (200 mg), dexclorfeniramine (5 mg), and ranitidine (50 mg), 0.7 mg of intramuscular epinephrine, fluid therapy, and nebulized budesonide and salbutamol. In the absence of improvement, the patient was admitted to the Critical Care Unit, improving within a few days. Serum tryptasewas not measured during the reaction.

Afterward, she was referred to our department, where an allergic study was performed 1 month after the reaction. After a detailed anamnesis, we excluded the simultaneous use of other drugs as well as the presence of possible co-factors, starting the allergologic investigation with a high suspicion of causality for the repellent solution applied to the skin. The basal serum tryptase level was normal (2.76 µg/L).

An open patch test was performed by applying a small drop of the Medcell® repellent solution in the forearm of the patient. Open patch test was performed in 5 atopic controls with negative result. Also, a BAT was performed with Medcell® repellent solution and with DEET. Whole blood was used, and both substances were tested in a dose-response curve using several dilutions. Double staining was performed with CD203c-PE to select the basophil population and CD63-FITC to measure basophil's activation.

Thus, the investigation was extended using a Dot Blot assay. The extracts, diluted in phosphate-buffered saline (PBS), were coated on a nitrocellulose membrane using a 96-well dot-blot system. The membrane was removed from the device and blocked in PBS-Tween 20 0.5% for 1 h at room temperature (RT). The membrane was then incubated with patient serum (dilution 1/5 in PBS-Tween 20 0.5%, overnight, 4ºC). Finally, a dot blot inhibition assay was performed. Patient serum (diluted 1/5) was pre-incubated for 30 min with different concentrations of DEET extract.

Open patch with a small drop of the Medcell® repellent developed erythema and papula of 6 × 3 cm within a few minutes. The CD63 BAT, conducted with Medcell® repellent solution and with DEET, showed a positive response for both DEET and Medcell® (Figure 1 and Figure E1 in the Online Repository).

Dot Blot assay was also positive for DEET and Medcell®. The recognition of the repellent solution in its entirety was greater thanthat of isolated DEET (Figure E2 in the Online Repository). Finally, the Dot Blot inhibition assay showed total inhibition of specific IgE to the repellent with DEET (Figure E3 in the Online Repository).

Based on the clinical history and allergologic study, our patient was diagnosed with an anaphylactic reaction to DEET. Subsequently, we advised the patient to check the excipients listed for all kinds of repellent solution that could contain DEET.

Hypersensitivity reactions associated with the DEET insect repellent application have been rarely described, with almost all cases being contact

urticaria [3-7] or urticaria [8]. Until now, Miller described in 1972 the only case of anaphylaxis to DEET. A 42-year-old woman touched a companion who had just sprayed himself with an insect repellent containing DEET. She suffered generalized pruritus, generalized angioedema, and nausea and, finally, lost awareess. In the Emergency Room, her blood pressure was 70/40 mm Hg [9].

Generally, detail anamnesis and skin test (open patch test in the forearm) has been the primary tool of diagnosis showing a relationship of causality with DEET application. Very few *in vitro* studies with DEET have been realized. Galassi et al. presented the first positive BAT to DEET in a case of contact urticaria with DEET. These authors presented a 50-year-old woman who had an urticarial reaction to multiple DEET-based insect repellents. She reported an urticarial rash on the exposed areas few minutes after the application of the spray, aerosol, or lotion insect repellent containing DEET [6]. Wantke et al. search for – with no success – the presence of specific IgE to DEET by ELISA [8]. These authors described a 4-year-old boy who, shortly after applying DEET (contained in an insect repellent called Anti-Muckenmilch®) to his legs and forearms, suffered generalized itch and urticarial and also wheezed and coughed for 30 min.

In conclusion, we reported a case of a very severe anaphylactic reaction to DEET contained in an insect repellent solution diagnosed by the clinical history and a positive open patch test, positive BAT to DEET, and dot blot assay, respectively. Besides, the dot blot inhibition assay showed total inhibition of specific IgE to the repellent with DEET. All these data suggest an IgE-mediated immunological mechanism. To our knowledge, this is the first case of an anaphylaxis reaction to DEET with a positive *in vitro* study.

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Conflicts of interest

All authors declare that they have not conflicts of interest.

Previous presentations

This clinical case was partially presented as a poster in the 2019 EAACI Congress at Lisboa.

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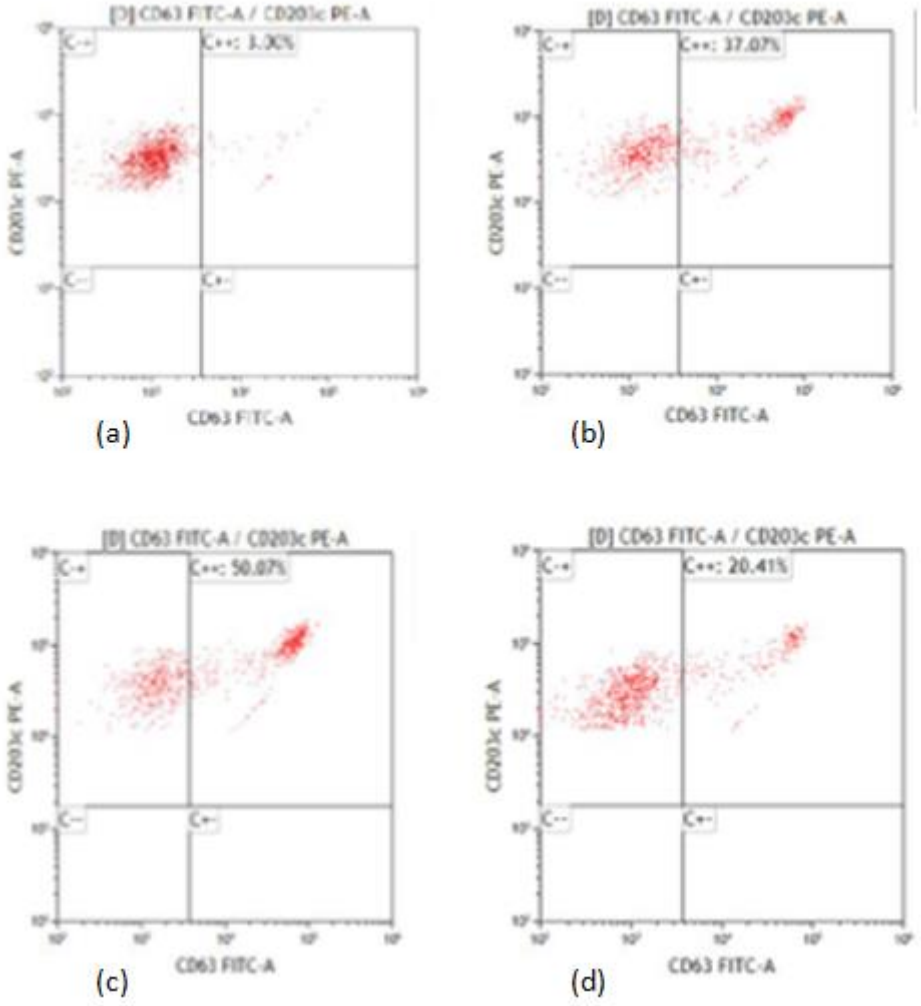
Figure 1. BAT with DEET and Medcell®



The C++ quadrant of the dot plots represents the percentage of basophils that expresses CD63 in high intensity (activation of cells). (a) Negative control; (b) positive control; (c) Medcell® at dilution 1/80; (d) DEET at dilution 1/80.

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