

Contact urticaria syndrome caused by polyaminopropyl biguanide in wipes for intimate hygiene

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Severe immediate-type allergic reactions to low molecular weight chemicals or protein-derived products in cosmetics are known, but are considered to be rare. Here, we describe a man who developed a severe immediate systemic reaction following the use of intimate hygiene wet wipes.

Case Report

A 39-year-old atopic (eczema and rhino-conjunctivitis) and diabetic (taking oral metformin) Caucasian man was referred in October 2012 with a history of anal pruritus, angioedema and general malaise following the use of wet wipes [Lilliput wipes® (Rossmann GmbH, Burgwedel, Germany)] for intimate hygiene, which had prompted him to visit the emergency department. The patient had already previously experienced minor symptoms when using the same wipes.

Patch tests were performed with the European baseline series, and both patch and prick tests with the wipes as such, as well as with the ingredients that were available, that is, phenoxyethanol 1% pet., *Chamomilla recutita* (German chamomile) 1% pet., *Anthemis nobilis* extract (Roman chamomile) 1% pet., and cocamidopropyl betaine 1% aq. (all from Chemotechnique, Vellinge, Sweden), propylene glycol 10% aq., allantoin 1% pet., and polyaminopropyl biguanide 1:10 aqua (the latter being in-house preparations). The positive and negative controls for prick testing were histamine and normal saline,



Fig. 1. Strong immediate positive prick test reactions to the wipes and to the ingredient poly(hexamethylene) biguanide [polyaminopropyl biguanide (INCI)], positive after 15 min, and increasing in intensity during the following 2 hr.

respectively. Chlorhexidine (1% aq.), another biguanide derivative, was also prick tested. Patch tests all gave negative results, whereas prick tests resulted in strong positive reactions after 15 min, which continued to increase in intensity during the following 2 hr, both to the wipes and to the ingredient poly(hexamethylene) biguanide (PHMB) (Fig. 1). The prick test with chlorhexidine gave a negative result.

A flow-assisted basophil activation test (BAT) (1, 2) with polyaminopropyl biguanide and chlorhexidine was positive for PHMB but negative for chlorhexidine. This test was also performed in 3 healthy control individuals, who had frequently been exposed to polyaminopropyl biguanide, but had not experienced any complaints as a result of this. Pre-warmed blood samples were stimulated with five different concentrations of polyaminopropyl biguanide (20, 4, 2, 0.4 and 0.2 ng/ml) diluted in an activation buffer. As a positive control, anti-human IgE (10 µg/ml; BD Biosciences, Aalst, Belgium) was used; activation buffer served as a negative control to measure

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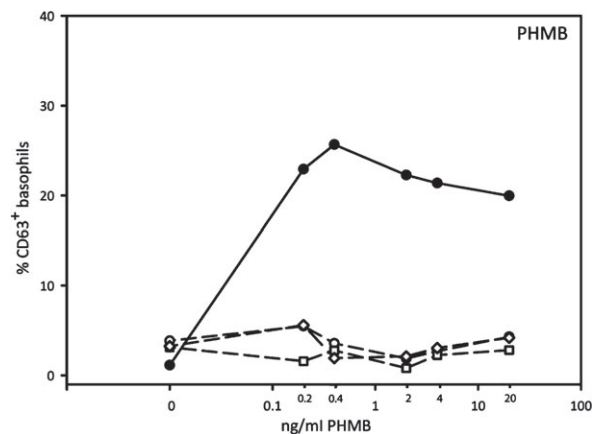


Fig. 2. Percentages of CD63⁺ activated basophils following stimulation with five different concentrations of poly(hexamethylene) biguanide (PHMB) [polyaminopropyl biguanide (INCI)] in the patient (solid line) and in 3 healthy exposed control individuals (dashed lines).

spontaneous CD63 expression. To analyse flow basophil activation cytometrically, cells were gated out by the use of side scatter, anti-IgE, and CD203c. Subsequently, within this gate, the activated basophils, that is, those expressing CD63, were measured. The results were expressed as the percentage of CD63⁺ basophils with subtraction of the negative control value. Figure 2 shows clear upregulation of CD63 upon stimulation of the patient's basophils with polyaminopropyl biguanide, in contrast to the healthy control individuals.

Polyaminopropyl biguanide was thus shown to be the cause of the contact urticaria syndrome in this patient; avoidance of contact with the wipes completely resolved his problem.

Discussion

Polyaminopropyl biguanide (INCI) (CAS nos. 32289-58-0; 70170-61-5; 133029-32-0; 28757-47-3), polyhexanide (INN) and PHMB (CAS no. 32289-58-0) are the names of a broad-spectrum, fast-acting bactericide that is now widely used as a preservative for cosmetics, such as make-up removers, toners, facial cleansers, and (baby) wet wipes; it is permitted at concentrations up to 0.3% according to Annex VI of the European Cosmetics Directive 76/768/EEC (3). It has also been used as a water disinfectant in the treatment of swimming pools.

In recent years, there has been increasing use of PHMB as wound care antiseptic solutions, gels, and dressings (4). Dissemond et al. recommended PHMB as the first choice for the treatment of critically colonized and locally infected acute and chronic wounds (5). It is also used in

non-alcoholic disinfectants and hand rub lotions, which are widely used in hospitals.

PHMB is the most frequently used antiseptic in traumatic and orthopaedic surgery, owing to its tissue compatibility (6). PHMB is an alternative preoperative antiseptic for iodine-intolerant patients in cataract surgery (7).

In 1975, Maibach and Johnson described the contact urticaria syndrome (8), which was subdivided into four different stages according to severity: stages 1 and 2 include only cutaneous reactions, whereas stages 3 and 4 also include extracutaneous reactions. Stage 3 includes bronchial asthma, rhino-conjunctivitis, and oro-laryngeal or gastrointestinal symptoms, and stage 4 includes anaphylactic reactions (9).

Four cases of contact urticaria syndrome caused by PHMB have been published in the literature; 3 cases occurred during surgery (10, 11), and the fourth on three different occasions, that is, from a wound dressing, from an antiseptic, and from wet wipes (12).

Olivieri described an 18-year-old woman and a 15-year-old boy who both had severe immediate reactions when a disinfectant containing PHMB (Lavasept®) was used to clean surgical wounds during orthopaedic surgery. Immediate-type hypersensitivity to PHMB was shown by positive prick test results. Both patients had previously been exposed to chlorhexidine, but prick testing with this gave negative results.

Ferrarini published a case of anaphylaxis during orthopaedic surgery in a 14-year-old boy following the perioperative use of a solution containing PHMB in the wound. Immediate-type hypersensitivity to PHMB was assumed, as no prick tests were performed.

Kautz described an 81-year-old woman with symptoms of a stage 3 contact urticaria syndrome following the use of a new brand of moist toilet tissue containing PHMB. She had previously experienced three episodes of minor symptoms caused by the same antimicrobial agent: a stage 2 contact urticaria syndrome caused by a wound dressing during wound care (Suprasorb®), and two episodes following the use of two different wound cleansing products (Lavanid® and Prontosan®). Prick tests with PHMB and chlorhexidine gave positive results, and ImmunoCAPs revealed specific IgE to PHMB and chlorhexidine. Kautz was able to demonstrate limited *in vitro* cross-reactivity, with higher avidity of the patient's IgE antibodies for PHMB than for chlorhexidine. Our patient did not react to chlorhexidine, either with prick testing or with the BAT. Chlorhexidine is also a biguanide, and is a well-known cause of IgE-mediated immediate skin reactions (13, 14).

Like chlorhexidine, metformin has two biguanidine groups. The development of angioedema immediately

after a single dose of metformin has been reported (15). Our patient, however, did not report any adverse side effects with this drug.

PHMB is a rare cause of delayed-type contact allergy. Indeed, positive patch test reactions were obtained with a very low frequency, namely 0.5%, and 0.4–0.8%, in consecutively patch tested subjects in studies by McFadden (16) and Schnuch et al., respectively (17, 18). More recently, it was shown to be an occupational allergen in a healthcare worker, owing to its use in a non-alcoholic rub (19), but also in wet wipes (20) and in a make-up remover (O Aerts, personal observation 2014).

According to the European Chemicals Agency, PHMB is severely irritant to the rabbit eye, but no classification was required for skin or respiratory irritation. On the basis

of both animal and human studies, PHMB was considered to be a sensitizer (21).

Conclusion

To our knowledge, this is the second report of severe contact urticaria syndrome (stage 3) caused by PHMB as contained in wet wipes with a confirmed IgE-mediated mechanism; although (partial) cross-sensitivity to chlorhexidine has been reported, this could not be established in our case.

As PHMB has been shown to have sensitizing properties, its increasing use in non-alcoholic disinfectants, as an antiseptic in wound care and also as a preservative in cosmetics requires surveillance of it as a possible emerging allergen.

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