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Systemic contact dermatitis of the eyelids caused by formaldehyde derived from aspartame?

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Formaldehyde is a common and ubiquitous contact allergen. Sources of exposure include hair and skin care products, cosmetics, topical medications, permanent press clothing, cleaning agents, disinfectants, paper and even smoke. Sensitization is reported in between 2.2 and 9.6% of patients patch tested(1,2).

Case Report

A 60-year-old Caucasian woman presented with a 6-month history of eyelid dermatitis. A corticosteroid-containing ophthalmologic ointment improved but did not clear the rash. She failed to improve when she discontinued the use of all eyelid cosmetics and nail polishes for 2 months. She had had a facial dermatitis in 1995, for which she had been patch tested and found to be allergic to Formaldehyde. She had also had incidental, non-relevant reactions to neomycin and ethylenediamine. Her dermatitis had resolved with a change to formaldehyde free facial and nail cosmetics.
There was no personal or family history of atopy or psoriasis. Her only oral medication was celecoxib that she had taken for years prior to the onset of her blepharitis. She had also taken multivitamins, calcium and flaxseed oil for many years. She worked as a homemaker and library volunteer. Her eyelid dermatitis was kept clear with tacrolimus 0.03% ointment X2 daily.
She underwent patch testing to the North American Contact Dermatitis Group standard tray, the University of Kansas' supplemental standard tray, and to her cosmetics, cleansers, skin and hair care products and topical medications. She had relevant positive reactions at days 2 and 4 to formaldehyde (++), quaternium-15 (++), diazolidinyl urea (+), DMDM hydantoin (+) and imidazolidinyl urea (++), her hair care products and cleansers containing multiple sources of these allergens.
She was extensively instructed in avoidance of formaldehyde and formaldehyde releasers, as well as that of her multiple, currently non-relevant allergens, including fragrance, benzalkonium chloride, neomycin, bacitracin, p-phenylenediamine and black rubber mix. By strictly avoiding formaldehyde and all formaldehyde releasers for the next 3 weeks, she improved only slightly.

Her problem, however, was subsequently solved when a local pharmacist advised her to avoid aspartame. She had begun using an aspartame-based artificial sweetener 5 months prior to the onset of her dermatitis. Within 1 week of discontinuing the aspartame, her eyelid dermatitis resolved completely and has not recurred over 18 months without specific treatment. Unfortunately, she refused to undergo rechallenge with the sweetener.

Discussion

The artificial sweetener, aspartame, is consumed by 54% of adults in the USA (3). It has been reported to cause dry eyes and difficulty in wearing contact lenses (3) but never allergic contact dermatitis. Aspartame, an L-aspartyl-L-phynylalanine methyl ester, is hydrolyzed in the intestine to phenylalanine (50%), aspartic acid (40%) and aspartic acid methyl ester (10%). The methyl ester is then converted to methyl alcohol (methanol) and carried by the portal vein to the liver. Methanol is there oxidized to formaldehyde that is converted into formic acid (formate) by alcohol dehydrogenase, aldehyde dehydrogenase and the microsomal oxidase pathway. This occurs not only in the liver, but also in other organs containing high levels of these enzymes, including the eye (4,5). Formaldehyde binds proteins and nucleic acids, forming adducts difficult to eliminate via metabolism.

Trocho et al. (6) demonstrated the formation of formaldehyde adducts with DNA and proteins after administration of 20 mg/kg 14C-labelled aspartame to rats, concluding that these adducts were responsible for functional alterations of proteins and for DNA mutations leading to autoimmunity, cell death or malignant transformation.

In contrast to Trocho et al. (6), McMartin et al. (7) studied formaldehyde levels after large doses (3,000 mg/kg) of 14C-labelled methanol and 14C-labelled formaldehyde in monkeys, which unlike rats are sensitive to the toxicities of methanol. No increased formaldehyde derived from methanol was found. High levels of formic acid were found in all monkeys that were given methanol or formaldehyde. Based on the work of McMartin and al. (7), Tephly (8) concluded that the radioactive carbon from methanol, which was found in DNA and protein by Trocho et al., was due to the normal physiologic flow of single-carbon units through the folate pathway. Stegink et al. (9) have shown that doses of 100 mg/kg or greater of aspartame are required to increase methanol blood levels (and thus, presumable formaldehyde formic acid levels) above control. This would be equivalent to consuming 35 cans of diet beverage at one sitting for a 70 kg person. Leon et al. (10) studied doses of 75 mg/kg of aspartame daily for 24 weeks and found no change in blood or urine methanol levels and no symptoms of methanol toxicity. The dose used in Leon's study is 25 times the 90th percentile daily consumption of aspartame (11). Our patient was consuming an average of 80 mg (1.13 mg/kg) of aspartame daily, well below the levels previously studied. However, it is possible that the eye, with its high level of metabolic activity, could be affected by methanol (and subsequently formaldehyde) released from these low levels of aspartame and respond as a localized target organ to minute amounts of her known allergen, formaldehyde, or its metabolite, formate. It is also possible that the amplifying effects of cell-mediated immunity might detect trace amounts of a chemical not identified by more standard assays, such as blood or urine levels. Such a hypothesis might explain why her dermatitis was limited to the eyelids and give clinical support to Trocho's theory of formaldehyde adducts. Unfortunately, without rechallenging her with aspartame, we cannot test this hypothesis.

Nonetheless, her long-lasting remission following discontinuation of aspartame intake suggests that its breakdown to formaldehyde may have been a possible mechanism for her prior blepharitis.

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