1: Dermatitis. 2008 May-Jun;19(3):E10-1. Links

Formaldehyde, aspartame, and migraines: a possible connection.

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Aspartame is a widely used artificial sweetener that has been linked to pediatric and adolescent migraines. Upon ingestion, aspartame is broken, converted, and oxidized into formaldehyde in various tissues. We present the first case series of aspartame-associated migraines related to clinically relevant positive reactions to formaldehyde on patch testing.

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Formaldehyde, Aspartame, and Migraines: A Possible Connection

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Abstract and Case Series

Abstract

Aspartame is a widely used artificial sweetener that has been linked to pediatric and adolescent migraines. Upon ingestion, aspartame is broken, converted, and oxidized into formaldehyde in various tissues. We present the first case series of aspartame-associated migraines related to clinically relevant positive reactions to formaldehyde on patch testing.

Case Series

Six patients (ages 16 to 75 years) were referred for evaluation of recalcitrant dermatitis. By history, five of the patients were noted to have developed migraines following aspartame consumption; the sixth reported dermatitis flares associated with diet cola consumption of ≥ 2 liters/day. All six patients had current environmental exposures to formaldehyde or formaldehyde-releasing preservatives in their personal hygiene products and/or regular consumption of "sugar-free food" artificially sweetened with aspartame. Based on their histories and clinical presentations, these patients were patch-tested with the North American Contact Dermatitis Group 65-allergen Standard Screening Series and selected chemicals from the University of Miami vehicle, fragrance, bakery, and textile trays.

All six patients had positive reactions to formaldehyde, and four had additional positive reactions to formaldehyde-releasing preservatives (FRPs). Expert counseling on allergen avoidance (including avoidance of formaldehyde, FRPs, and aspartame) and alternative product recommendations were provided to the patients.

At their follow-up appointments (between 8 and 12 weeks), all the patients showed clearance of their dermatitis. Four patients (two inadvertently) resumed their consumption of aspartame and subsequently returned for an additional follow-up visit. Three of the first five patients had recurrences of both their migraines and their dermatitis; the sixth patient (who had no migraines) had a positive rechallenge dermatitis. These four patients were again counseled on avoidance regimen.

Discussion

Aspartame is a widely used artificial sweetener that has been linked to a multitude of ailments, particularly pediatric and adolescent migraines[1] (Table 1 and Table 2).[2-4] Studies suggest that aspartame is a significant migraine trigger, especially when consumption is prolonged.[1] Upon ingestion, aspartame is broken down into aspartic acid, aspartic acid methyl ester, and phenylalanine in the gut wall.[5] The methyl ester is subsequently converted into methanol, which is oxidized to formaldehyde and formic acid in various tissues.[6] Formaldehyde is known to form chemical adducts with nucleic acids and proteins. These adducts have been found to be difficult to remove by normal metabolic pathways; hence, accumulation may occur.[6]

To our knowledge, aspartame-associated migraines related to clinically relevant positive reactions to formaldehyde on patch testing have not previously been reported. In 2003, Hill and Belsito reported a case of a nonmigraine patient with chronic eyelid dermatitis that cleared when aspartame was discontinued. This case presented the possibility that formaldehyde from aspartame breakdown could trigger a systemic contact dermatitis in formaldehyde-sensitive patients.[7] Like Hill and Belsito's patient, our sixth patient (the only patient who did not have migraines) demonstrated a flare of his dermatitis with consumption of aspartame and clearance with avoidance of aspartame. Our five migraine cases suggest that aspartame-induced migraines may be a harbinger for formaldehyde sensitivity and an important historical point to be elucidated during the initial work-up of a patient with presumed allergic contact dermatitis.

Although we recognize the limitations of drawing conclusions from a small sample of patients, we believe this observed association warrants further investigation. A larger case study with a double-blind placebo-controlled challenge study with aspartame capsules and placebo capsules (including nondermatitic control patients with aspartame-induced migraines) is needed to firmly establish the association between aspartame breakdown products, migraines, systemic contact dermatitis, and positive patch-test reactions to formaldehyde and FRPs.

Table 1. Aspartame in Foods and Drinks

Food or Drink	Average Amount of Aspartame per Unit
Carbonated soft drink	180 mg/12 oz can (354 mL)
Yogurt	124 mg/8 oz (237 mL)
Powdered soft drink	120 mg/12 oz (354 mL)
Gelatin	95 mg/4 oz (118 mL)
Fruit drink (10% juice)	70 mg/6 oz (177 mL)
Ice cream	50 mg/4 oz (118 mL)
Hot chocolate	50 mg/6 oz (177 mL)
Chewing gum	6–8 mg per stick
Chewable children's vitamins (Flintstones Vitamins, Bayer, Morristown, NJ)	4 mg per vitamin
Breath mints	1.5 mg per mint

Table 2. Artificial Sweetener Brand Names

Artificial Sweetener	Brand Names
Aspartame	Equal, NutraSweet
Sucralose	Splenda
Saccharin	Sweet 'N Low, Sweet Twin, Necta Sweet, Hermesetas
Acesulfame potassium	AceK, Sweet One, Sunett
Cyclamate	Sugar Twin, Sucaryl, Weight Watchers TM

Neotame	No Name Brand

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To the Editor,

Thank you for the comments received regarding the potential association of aspartame consumption with migraine headaches and recurrent allergic contact dermatitis (ACD).
While the commentary did not address the key issues of our observations [ie, that challenge results in a response and that a patch test challenge with formaldehyde was positive], we appreciate the opportunity to discuss this further.[1]
Molecule for molecule, 11% of aspartame that is hydrolyzed becomes methanol (wood alcohol) in the blood.[2]
The commentary authors' statement suggests that methanol metabolism is very rapid; however, the Environmental Protection Agency has reported methanol to in fact be a cumulative toxin.[3]
It is true that methanol is generated from food, but the average intake of methanol from natural sources is reported to be about 10 mg/day, while a 12 ounce aspartame beverage generates 56 mg/L of methanol, or 22 mg per 12 ounces if fully hydrolyzed.[4]
More than 30 years ago, Oppermann and colleagues reported that there was 31% retention of radioactive methanol in rats 8 hours after ingestion, retention levels confirmed by an expert review of modern studies by M Bouchard and colleagues in 2001.[5],[6]

The administration of radiolabeled aspartame to experimental animals has been shown to result in the incorporation of a significant proportion of the label into proteins (thought to be the result of the formation of formaldehyde and formate adducts) at least six hours after aspartame ingestion.[7]
In this study, the liver was found to retain more than 2% of the

methanol carbon from a single dose of aspartame![7]
Cumulative effects data obtained from the chronic administration model also have suggested that regular intake of aspartame may also result in a progressive accumulation of formaldehyde adducts.[7]

Furthermore, it is important to note that the commentary authors' reference to the assumption that the incorporation of the methanol carbon to normal amino acid structures through the "essential one-carbon" tetrahydrofolate and S-adenosyl-methionine pathways from aspartame consumption is an assumption no longer maintained according to current data. [7]

In their discussion, the commentary authors raised several false premises.
For example, they concluded that aspartame does not cause allergic-type reactions, based on a study that demonstrated that aspartame and its conversion products were no more likely than placebo to cause urticaria, angioedema reactions, or both, which ignored delayed-type hypersensitivity reactions altogether.[8]
It is important to recognize that ACD is an allergic-type reaction with an entirely different mechanism (type IV T-cell mediated reaction) from the type I reactions referenced.[9] And notably, aspartame has been previously associated with ACD.[10]

Furthermore, if the incidence of this aspartame-mediated migraine response is one in a thousand, then a random study group size would need to be much larger than the ones cited by Schiffman and colleagues and Leon and colleagues. It is important to note that both Schiffman and colleagues (1987) and Leon and colleagues (1987), did not study the formaldehyde allergic patient[11],[12] and, that without knowing the true incidence of aspartame sensitivity in dermatitis patients, it is impossible to make any conclusion from these studies.

We absolutely recognize the need to further study the biochemistry of these reactions and that there is speculation and concern about aspartame's being a sufficient source of formaldehyde to evoke the response, especially when wine and many foods contain methanol and methyl esters.
This being said, we believe the dose may be critical and question the

effect of ingestion of aspartame as a bolus, as foods are generally more slowly metabolized.
Last, the dose levels of aspartame needed to provoke a response in an exquisitely sensitized person may be very low, making half-life and metabolic rate less meaningful.

Thank you for this opportunity for intellectual discourse.
We still maintain that a larger case study including aspartame-induced migrainous non-dermatitis control patients is necessary to establish the association presented in our study, and we would like to perform an aspartame-formaldehyde challenge to show repeatable responses. Alternatively, we would like to challenge individuals known to have formaldehyde sensitivity with aspartame and demonstrate a response as an indirect proof of principle.

Acknowledgments

We acknowledge Tony E. Hugli, PhD, of the Torrey Pines Institute for Molecular Studies, for his provocative academic discourse on the metabolism of aspartame as we work toward better understanding this observed phenomenon.

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"For example, fruit juices, coffee, and alcoholic beverages produce
significantly greater quantities of formaldehyde than aspartame-
containing products. [6]"

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safety evaluation based on current use levels, regulations, and

toxicological and epidemiological studies.
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[two detailed critiques of industry affiliations and biased science in 99 page review with 415 references by BA Magnuson, GA Burdock and 8 more, Critical Reviews in Toxicology, 2007 Sept.: Mark D Gold 13 page: also Rich Murray 2007.09.15: 2008.03.24
http://rmforall.blogspot.com/2008_03_01_archive.htm
Monday, March 24, 2008
http://groups.yahoo.com/group/aspartameNM/message/1531

"Nearly every section of the Magnuson (2007) review has research that is misrepresented
and/or crucial pieces of information are left out.

In addition to the misrepresentation of the research,
readers (including medical professionals) are often not told that this review was funded by the aspartame manufacturer, Ajinomoto, and the reviewers had enormous conflicts of interest."]
