

Treating chronic spontaneous urticaria in children



To the Editor:

The recent review of pediatric urticaria discussed the use of antihistamines for the treatment of urticaria.¹ This subject deserves additional details regarding the relative efficacy of these medications. Studies had previously demonstrated that the relative efficacy of hydroxyzine exceeded that of other antihistamines.² Because the active metabolite of hydroxyzine is cetirizine, those data also support the greater efficacy for cetirizine (Figure 1).³ Levocetirizine, the active optical R-enantiomer of racemic cetirizine, is equivalent to racemic cetirizine, containing an equimolar amount of the R-enantiomer.⁴

Also relevant is the dose-response of antihistamines. Increasing the dose of antihistamines to 4 times usual dosage is common practice. Levocetirizine, the active enantiomer of cetirizine, at doses of 5 to 20 mg (the molar equivalent of 20-40 mg racemic cetirizine), was compared with the same milligram doses of desloratadine, the active metabolite of loratadine. A progressive increase in the dose-response effect of levocetirizine, but not for desloratadine, was seen.⁵ On the basis of evidence, cetirizine (or its active enantiomer alone, levocetirizine) is likely to be the most effective antihistamine for chronic urticaria.

The recent review of urticaria¹ also included the rate of spontaneous resolution of chronic urticaria in adults but not for children. However, published data from 92 children found remissions of

19%, 54%, and 68% at 1, 3, and 5 years, respectively.⁶ Although omalizumab provides symptomatic improvement of chronic urticaria, symptoms return when the treatment is stopped. In contrast, cyclosporine provided prompt control of chronic urticaria with sustained remissions.⁷ Safety and efficacy in the pediatric study used the reliably absorbed microemulsion formulation of cyclosporine with therapeutic drug monitoring targeting serum concentrations of 100 to 200 ng/mL. With that strategy, prompt elimination of urticaria occurred and continued for most following rapid cessation of the cyclosporine.

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Conflicts of interest: The author declares no relevant conflicts of interest.

Received for publication April 7, 2018; accepted for publication May 1, 2018.

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<https://doi.org/10.1016/j.jaip.2018.05.003>

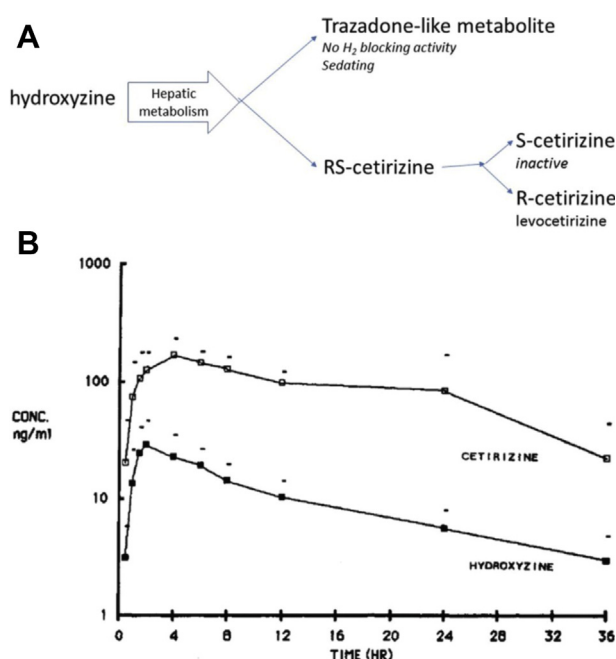


FIGURE 1. A, Metabolism of hydroxyzine to racemic cetirizine (RS-cetirizine) and a metabolite with sedation but no antihistaminic effect. Racemic cetirizine can be separated into the individual enantiomers, the inactive S-cetirizine and the active R-cetirizine. B, Mean cetirizine and hydroxyzine serum concentrations following administration of 25 mg hydroxyzine to 25 adult male volunteers (reproduced with permission from Gengo et al³). HR, hours.

Reply



To the Editor:

In his commentary, Weinberger¹ levied several critiques on our review² of the management of chronic urticaria (CU) in children, which we address below.

His first point relates to the premise that the relative efficacy of hydroxyzine exceeds that of other antihistamines. However, the referenced study assessed only the effect of hydroxyzine on allergen and histamine-induced skin prick test size³ rather than any effect on hives in the setting of CU, which might involve different pathogenic mechanisms. Numerous reviews and clinical trials support the use of second-generation rather than first-generation antihistamines due to similar efficacy but better safety profile.⁴ In clinical trials, including multicenter, double-blind, placebo-controlled studies, the safety and efficacy of cetirizine (a second-generation antihistamine) and hydroxyzine is similar and cetirizine has a greater safety margin over the older parent drug hydroxyzine.^{5,6} A systematic Cochrane review concluded that there is no difference in short-term treatment between

loratadine (10 mg) and hydroxyzine (25 mg) in terms of complete suppression of CU symptoms and that no single H1 antihistamine stands out as most effective.⁷ The figure⁸ that Weinberger presents relates to cetirizine and hydroxyzine concentrations rather than efficacy and appears to show a high conversion of the parent drug to its primary metabolite. This study again concludes that cetirizine is superior to hydroxyzine because it produced an equivalent suppression of skin wheal response to histamine versus placebo but, unlike hydroxyzine, did not produce significant central nervous system effects. Specifically, this study did not conduct a comparison with other second-generation antihistamines. The Ino et al⁹ study quoted by Weinberger was conducted in adults and the authors acknowledge that the small sample size and single-dose design of this study prevent definitive conclusions regarding the pharmacokinetics and safety of levocetirizine.

The second point refers to up dosing of antihistamines. Weinberger argues that increasing the dose of antihistamines to 4 times the usual dosage is common practice. We address this point in our review: “according to current European, Canadian and WHO guidelines, the dose of second-generation antihistamines should be increased up to four times for a trial if the standard dose is not effective.”¹⁰⁻¹² We also point out that only limited studies have been conducted in adults to support this practice.^{13,14} Given that these studies, including the Staevska et al¹³ study, referred to by Weinberger, were conducted in adults, the findings cannot be generalized to CU in the pediatric population¹³ although they may be applicable in children based on extrapolated data from rhinitis studies.¹⁵ It is crucial to assess the practice of increasing 4 times the dose in the pediatric population, given that studies suggest that in teenagers and adults, cetirizine promoted somnolence and decreased motivation to perform activities during the workday compared with loratadine, even at recommended doses.^{16,17}

The third point raised relates to the rate of CU resolution in children. Weinberger claims that the review included the rate of spontaneous resolution of CU in adults and not children. However, the resolution estimate provided was based on the largest (139 children) pediatric cohort to assess CU resolution.¹⁸ As quoted in the review, the natural resolution rate of CU in a cohort of Canadian children was relatively low (10% per year).¹⁸ In contrast, the higher resolution rate quoted by Weinberger was for a smaller cohort (92 children) with a more limited age range (4-15 years) and included patients with food allergy and/or parasite infections (almost 10% of this cohort).¹⁹

His last comment refers to the remission rate with ciclosporin. He suggests that in contrast to omalizumab, ciclosporin provided prompt control of CU with sustained remission.²⁰ This is potentially important. However, the study cited had several flaws and hence conclusions regarding long-term effects of ciclosporin are not conclusive. It was not a randomized controlled trial but rather a retrospective examination of data and hence subjected to potential bias and confounding. The study did not compare omalizumab and ciclosporin head to head. Moreover, the authors indicate that the resolution of CU lasted between 2 days and 3 months (median, 7 days) and relapses were responsive to repeated ciclosporin in 5 of the patients after 1 week to 15 months (median, 6 months).²⁰ Given that complete resolution has been defined as absence of symptoms and no need for medications for at least 1 year,¹⁸ the study cited does not establish a long-term beneficial effect of ciclosporin. A larger, more recent, study specifically assessing CU relapse in a larger sample of adults (93 vs 46) after

omalizumab treatment revealed that 3 months after the start of treatment, 44 (47%) patients had a complete response and 36 (39%) patients had a partial response.²¹

We believe that the conclusions raised in our review are well supported by the current literature although more studies are needed: second-generation antihistamines should be used as first-line treatment for pediatric CU, and there is a low resolution rate (relatively low [10% per year]) of pediatric CU, with insufficient evidence for long-term effects of omalizumab or ciclosporin.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication April 30, 2018; accepted for publication May 1, 2018.

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<https://doi.org/10.1016/j.jaip.2018.05.002>

Possible contribution of decreased phytoprostanes to diet-induced improvements in aspirin exacerbated respiratory disease



To the Editor:

The pilot study showing the potential of dietary changes to affect aspirin-exacerbated respiratory disease (AERD) is an important step toward understanding and exploiting the role of diet in the treatment of asthma and rhinitis.¹ As the authors point out, the greatly increased consumption of vegetable oils has caused an increase in omega-6 fatty acids including arachidonic acid, the precursor of prostaglandins and leukotrienes. However, we should not assume that all of the improvement in this study resulted solely from the decrease in the ratio of omega-6 to omega-3 fatty acids. It is also plausible that benefits accrued from a decreased intake of plant phytoprostanes present in plant oils.

Although the enzymatic modification of omega-6 arachidonic acid to prostaglandins (via cyclo-oxygenase) and to leukotrienes (via lipoxygenase) is doubtless important, it should be noted that there is also a non-enzyme-mediated pathway of arachidonic acid metabolism in humans, wherein arachidonic acid is converted by free-radical oxygenation to a third class of inflammatory mediators, the isoprostanes.² Isoprostane F₂ is present in exhaled breath condensates of patients with asthma in proportion to the asthma's severity and increases in the urine of asthmatics after allergen challenge.³ Plants produce proinflammatory analogs of isoprostanes, the phytoprostanes, which are also the products of nonenzymatic oxidation, but in this case of the plants' 18-carbon omega-3 alpha-linoleic acid.²

High levels of alpha-linoleic acid are present in vegetable oils, and its auto-oxidation leads to the formation of phytoprostanes in those oils.⁴ Studies have found high levels of proinflammatory F₁ and E₁ phytoprostanes in all oils examined, including olive oil, with levels of phytoprostanes in opened bottles of vegetable oils at room temperature spontaneously increasing 10- to 20-fold over 18 days, despite a lack of noticeable rancidity. When humans ingest these oils, including olive oil or flaxseed oil, their level of serum phytoprostane F₁ increases.^{4,5}

The current typical Western diet has changed in many ways from that present during human evolution.⁶ In the last 70 years alone, the intake of refined vegetable oils has increased from less than a pound to over 50 lbs per person per year in the United States,⁶ thus increasing not only the ratio of n-6 to n-3 fatty acids but also the amount of ingested phytoprostanes. Whole plants differ from separated plant oils in that the whole plant contains

antioxidants that minimize oxidative damage, including the formation of phytoprostanes. There are strong reasons to believe that a *whole-food*, plant-based diet is the diet most compatible with human health.⁷

The authors have made an important contribution and have avoided the common error of simply adding a "supplement" rather than changing the diet as a whole. Nevertheless, future studies may want to consider removing flaxseed and olive oils from the "recommended" and "limit" categories, and placing them with the other separated vegetable oils in the "discouraged" column.

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No funding was received for this work.

Conflicts of interest: J. D. Miller is the owner and President of Mission: Allergy, Inc.

Received for publication May 18, 2018; accepted for publication May 22, 2018.

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<https://doi.org/10.1016/j.jaip.2018.05.033>

Indoor environmental interventions for furry pet allergens: How to decrease the degree of passive transport



To the Editor:

We read with interest the excellent article of Ahluwalia and Matsui¹ focusing on interventions for indoor environmental allergens. In the section of "furry pet allergens," the authors have considered predominantly the case of pets at home only hinting at the problem of passive transfer of pet allergens indoors. Although the authors have indicated that pet allergens are carried and passively transferred to environments where no pets may be present, they have not provided any indication on the possible modalities of prevention. Conversely, we believe that this is a central and difficult-to-manage aspect in the context of pet allergy with or without animals at home.^{2,3} In fact, deposit of pet allergens in indoor environments without animals correlate with the number of visitors owning or in regular contact with pets. Therefore, the higher the pet ownership in a given community, the higher the presence of pet allergens in apparently pet-free spaces. We⁴ and others have shown that clothing