

Might the Use of Acid-Suppressive Medications Predispose to the Development of Eosinophilic Esophagitis?

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The prevalence of eosinophilic esophagitis, a manifestation of food allergy, has increased in recent years for reasons that are not clear. The gastrointestinal mucosa is regularly exposed to food antigens with the potential to evoke immunological reactions. Studies have shown that some food allergens that ordinarily would be degraded by peptic digestion are not degraded when the pH of gastric fluid is raised to levels commonly found in the stomachs of patients treated with proton pump inhibitors (PPIs). Other studies have shown that PPIs increase gastrointestinal mucosal permeability, which might facilitate the uptake of undegraded peptide allergens. Mice treated with antisecretory medications while being fed a diet of caviar have been found to develop caviar-specific immunoglobulin E (IgE) antibodies, T-cell reactivity, and gastric eosinophilia. Adult patients treated with antisecretory medications for 3 months have been found to develop a rise in their IgE antibody levels and new, food-specific IgE antibodies. These data establish a plausible mechanism whereby acid-suppressive medications, by interfering with the peptic digestion of food allergens and increasing mucosal permeability, might lead to the development of food allergy. The time course of the introduction and subsequent widespread usage of PPIs with the emergence of eosinophilic esophagitis fits well with the hypothesis that PPIs may play an etiological role. Although the mere demonstration of a plausible association does not establish cause and effect, further studies on the role of acid suppression in the development of eosinophilic esophagitis clearly are warranted.

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Physicians should be aware of emerging data suggesting a potential role for antisecretory medications in the pathogenesis of certain types of food allergy. Definitive data on the prevalence of food allergy in general are not available (1), but the reported prevalence of eosinophilic esophagitis, which appears to be a manifestation of food allergy, clearly has increased in recent years in parallel with the widespread use of potent antisecretory agents such as histamine H₂-receptor antagonists and proton pump inhibitors (PPIs) (2). Such an association does not establish cause and effect, and by no means is it clear that those medications have contributed to the rising frequency of any form of food allergy. Nevertheless, recent studies have elucidated a plausible mechanism whereby antisecretory agents, by interfering with the peptic digestion of dietary proteins and by increasing mucosal permeability, might predispose to food allergy (3,4). This report reviews those data and their clinical implications.

Protein digestion

Most recognized food allergens are glycoproteins that are derived from animals and plants (5). Swallowed glycoproteins pass relatively quickly through the esophagus to enter the

stomach, and the normal esophageal squamous epithelium is highly impermeable to such large molecules. For example, Tobey *et al.* found that normal rabbit esophageal squamous epithelium was virtually impermeable to epidermal growth factor, a peptide with a molecular weight of 6 kDa, and to dextrans with a molecular weight of 4 kDa (6).

Protein digestion normally begins in the stomach through the action of proteinases that are secreted into the gastric juice. Humans secrete at least seven different proteinases, which have distinctive chemical properties that enable the digestion of a variety of proteins (7). The pepsin proteinases are synthesized by gastric chief cells in the form of inactive precursors called pepsinogens. Acid in the stomach initiates the process that converts pepsinogens into active pepsins (8,9). The optimal pH for the enzymatic activity of the pepsins is between 1.8 and 3.2, and most of their proteinase activity ceases at pH levels above 4.5 (7,10). The sizes of the fragments produced by the peptic digestion of dietary proteins vary considerably. In the case of bovine B-casein, for example, peptic digestion results in peptides with sizes ranging from 2 to 36 amino acids in length (11).

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The protein fragments generated by peptic digestion in the stomach are transported into the duodenum, where acid is neutralized by bicarbonate secreted from the pancreas and the small intestine. Peptic digestion ceases in this alkaline environment, where pancreatic proteinases and peptidases on the enterocyte surface digest the protein fragments into amino acids and oligopeptides that can be taken up by the enterocytes. These products of protein digestion can be absorbed throughout the small intestine, but most dietary protein is absorbed in the duodenum and jejunum (12,13).

A small percentage of ingested protein escapes digestion by gastric and pancreatic proteases and can be absorbed intact or in the form of large protein fragments that have the potential to induce an immune response. After the oral administration of ovalbumin, for example, small amounts of the intact protein can be found in the plasma and in lymphatic fluid, and some of this intact ovalbumin absorption appears to occur in the stomach (14,15). The absorption of intact peanut proteins through the oral mucosa also has been described (16). The precise contribution of this phenomenon to the development of food allergy is not clear.

Oral tolerance vs. immunogenicity

The gastrointestinal tract, with its 400 m² of mucosal surface area, might be considered the largest immune organ of the body (17,18). The extensive gastrointestinal mucosal surface regularly is exposed to food, microbes, and other foreign antigens that might trigger hypersensitivity reactions. Fortunately, tolerance is the predominant immune response evoked by the large majority of ingested antigens (19). Oral tolerance is defined as the specific suppression of cellular and/or humoral immune responses to an antigen produced by prior exposure to the antigen through the oral route. The mechanisms whereby dietary antigens induce tolerance rather than hypersensitivity and allergy are not well understood but appear to involve complex interactions among intestinal epithelial cells, dendritic cells, microfold (M) cells, and regulatory T cells (11,17,20). The integrity of the intestinal epithelial barrier also appears to play a role in oral tolerance, with gut barrier dysfunction predisposing to the development of food allergy (21,22).

The immunological response to an ingested antigen depends in part on the physical nature of the antigen and its route of absorption in the gut (23). Particulate antigens, which often are associated with microbial pathogens and which commonly are taken up by M cells of the follicle-associated epithelium, are frequently immunogenic. In contrast, soluble dietary antigens, which are commonly taken up and presented to immune cells by enterocytes, often induce tolerance. There appear to be exceptions to this pattern, however. For example, the transport of soluble peanut protein by M cells of the follicle-associated epithelium has been demonstrated (24). It is not clear whether this route of absorption contributes to the development of peanut allergy.

Immune tolerance can occur in the form of a regulatory cell-driven tolerance, in which the antigen induces T cells that secrete downregulatory cytokines such as interleukin-10 and

interleukin-4, or an anergy-driven tolerance, in which the antigen causes a loss of T-cell function. In general, low doses of antigen favor the generation of regulatory cell-driven tolerance, whereas high doses predispose to anergy-driven tolerance (25).

Typical food allergens have a molecular weight between 3 and 90 kDa (26). Smaller peptides may not be capable of inducing an immunological response. Indeed, the minimum molecular weight required for whey peptides to elicit an immunological response was found to be between 3 and 5 kDa (27). A peptide's ability to bind immunoglobulin E (IgE), a frequent feature of food allergens, also can be diminished by partial digestion of the peptide to a smaller size. In a study of animals that were immunologically sensitized to a whey protein, for example, the intravenous administration of a whey protein hydrolysate with a molecular weight of 3 kDa failed to induce an IgE-mediated allergic reaction (28). The class I major histocompatibility complex typically presents peptides comprising 8 to 10 amino acid residues to cytotoxic T lymphocytes, and smaller peptide fragments may be ignored by the immune system (11,29). These data suggest that food proteins that are rapidly digested into individual amino acids, dipeptides, and tripeptides would be unlikely to induce any immunological response.

On the basis of the above observations, it is conceivable that proteins that are resistant to peptic digestion might be especially immunogenic. In 1996, Astwood *et al.* reported that soybean allergens and peanut allergens were resistant to digestion by simulated gastric fluid (SGF), which contained acid and pepsin, whereas a number of nonallergenic food proteins were rapidly degraded in SGF (30). However, other investigators have challenged those findings, noting rapid digestion of plant allergens in SGF (31,32).

It remains unclear whether resistance to peptic digestion under normal conditions is an important feature of food allergens. However, acid-suppressive medications such as PPIs can raise the gastric pH to levels at which pepsin is not active (10). Under those circumstances, dietary proteins that normally would be partially digested in the stomach can reach the duodenum largely intact. Conceivably, that might expose the small intestine to food allergens that ordinarily would have been destroyed by peptic digestion and, thereby, predispose to the development of food allergy.

Effects of PPIs on gastrointestinal mucosal permeability

One group of investigators recently found that their patients with reflux esophagitis and Barrett's esophagus, many of whom were taking antisecretory medications, had abnormal sucrose permeability tests, indicating increased permeability in the mucosa of the upper gastrointestinal tract (33). In a subsequent study, the same investigators performed sucrose permeability tests in gastroesophageal reflux disease (GERD) patients before and after 8 weeks of treatment with the PPI esomeprazole (4). Although the researchers hypothesized that PPI treatment should improve mucosal barrier function, they were surprised to find that most patients exhibited

a substantial increase in mucosal permeability to sucrose after PPI treatment. This unanticipated finding was confirmed in a group of healthy control subjects who also developed abnormal sucrose permeability tests during 9 days of PPI treatment. Within 4 days of stopping the PPI, furthermore, their sucrose permeability returned to near normal levels. In earlier studies, another group of investigators found that rat stomachs that had been stimulated to secrete acid by the administration of histamine, developed a significant increase in mucosal permeability when treated with omeprazole (34).

Further studies are needed to elucidate the mechanism whereby PPIs cause increased mucosal permeability in the upper gastrointestinal tract. Nevertheless, PPI-induced increases in mucosal permeability conceivably could contribute to the development of food allergy. In patients taking PPIs, large and potentially allergenic peptides that escape peptic digestion because of acid inhibition could be taken up through the PPI-induced mucosal leak to elicit an immunological response.

Evidence that antisecretory medications predispose to food allergy

In 2002, Eva Untersmayr and her colleagues in Vienna reported a patient who developed anaphylaxis to Beluga caviar, a food previously not known to cause anaphylaxis (35). Skin prick testing indicated that the patient was allergic to caviar proteins, which were found to be rapidly degraded by SGF (26). Subsequently, it was learned that the patient was taking acid-suppressive medication for the treatment of gastric ulcer. This prompted the investigators to explore the possibility that antisecretory medications might contribute to the pathogenesis of food allergy.

Untersmayr's group found that the peptic digestion of codfish allergen is exquisitely sensitive to small variations in the pH of SGF (36). IgE antibodies in the sera of patients with codfish allergy bind to a 10-kDa peptide band in undigested cod extract. This peptide allergen is rapidly digested in SGF that has a pH ≤ 2.5 , and the digested codfish protein exhibits dramatically reduced allergenic potency as evaluated by radio-allergosorbent testing and by histamine release from human basophils. However, when the pH of the SGF is raised to 2.75, a gastric pH level regularly exceeded in patients on PPI therapy, digestion of the codfish allergen is completely abrogated. Another study of patients with codfish allergy found that fish extracts digested with gastric enzymes at pH 2.0 have far less allergenic potency than undigested fish extracts as assessed by histamine release, skin prick tests, and titrated double-blind placebo-controlled food challenges (37).

In a BALB/c mouse model, Untersmayr studied the effects of antiulcer medications on the allergenicity of caviar proteins and parvalbumin, the major fish allergen (38). These proteins were found to undergo rapid digestion in SGF at pH 2.0, but not at pH 5.0, a pH level commonly found in the stomachs of patients on antisecretory medications (10). Untreated control mice that were fed caviar manifested no evidence of food allergy, whereas animals treated with ranitidine developed caviar-specific IgE

antibodies, T-cell reactivity, and gastric eosinophilia. Mice treated with ranitidine or omeprazole also developed allergen-specific IgE antibodies when they were fed parvalbumin. In a similar study using hazelnut allergens, which are also readily digested in SGF with a pH less than 3.0, mice were fed hazelnut extract alone or in combination with antiulcer medications (sucralfate orally or omeprazole intramuscularly) (39). Seven of ten mice taking antiulcer medications developed anaphylactogenic IgG1 toward hazelnut, and four developed type I skin reactivity to hazelnut extract. In contrast, none of five mice fed hazelnut extract alone developed IgG1 or skin reactivity to hazelnut allergens.

To seek an effect of antisecretory medications on food allergy in humans, Untersmayr and her colleagues studied serum IgE levels in 152 adult outpatients who had no history of allergy and who were treated with a histamine H_2 -receptor antagonist or a PPI for 3 months (40). A control group of 50 patients who were not taking antisecretory medications had IgE levels measured at baseline and 8 months later to detect IgE changes that might result from seasonal exposure to pollens and other environmental antigens. No significant changes in IgE levels were found in this control group. After 3 months of treatment of the patients with antisecretory medications, in contrast, 10% exhibited a rise in IgE antibody levels, and new, food-specific IgE antibodies developed in 15%. For the patients on antisecretory medications, this represented a relative risk for the development of food-specific IgE antibodies of 10.5 (95% confidence interval 1.44–76.48). In a similar study evaluating the development of hypersensitivity to hazelnut allergens in outpatients taking antisecretory medications for 3 months, five of 153 (3.3%) patients developed hazelnut-specific IgE antibodies; four of those developed specific skin reactivity, and two manifested clinical food allergy to hazelnuts (39).

Antisecretory medications and eosinophilic esophagitis

In the mid-1970s, the histamine H_2 -receptor antagonist cimetidine was the first antisecretory agent introduced into clinical practice in the United States. These agents rapidly emerged as the treatment of choice for peptic ulcer disease and GERD. The PPI omeprazole was released for clinical use in the late 1980s, and, today, PPIs are among the most commonly used medications in the world (41,42). PPIs are used regularly, not only in adults, but often in young children with GERD, who commonly take these medications for years (43,44).

PPIs are highly effective at inhibiting gastric acid production. After 5 days of conventional-dose PPI therapy, gastric pH rises to levels above 4.0 for approximately 50% of the day (45). With higher doses, as are prescribed often in clinical practice, gastric pH levels can remain above 4.0 for more than 80% of the day (46). At these pH levels, there can be little peptic digestion of a number of potential food allergens that normally would be partially degraded in the stomach.

Eosinophilic esophagitis appears to be a modern disorder that was not even described until the late 1970s and early 1980s, when early investigators thought that it was primarily

a variant of eosinophilic gastroenteritis (47,48). Before 1995, there were only 12 publications describing the disorder (49). Today, a PubMed search shows more than 400 publications on eosinophilic esophagitis. The limited epidemiological data that are available describe a dramatic rise in the frequency of this disorder over the past decade, although it is difficult to ascertain how much of this apparent increase in frequency is the result of increased physician recognition rather than a true increase in the frequency of the disorder (2,50). The rapid emergence of eosinophilic esophagitis approximately one decade after PPI usage became widespread, especially among children, would fit well with a PPI-associated, food-allergic disorder.

In eosinophilic esophagitis, eosinophils infiltrate the esophageal epithelium for reasons that are not clear, resulting in symptoms and epithelial injuries that are mediated by the release of cytokines from the eosinophils and surrounding tissues (51). Eosinophilic esophagitis is widely regarded as an allergic disorder. Patients commonly have a personal and family history of allergic disorders such as asthma, atopic dermatitis, eczema, and allergic rhinitis. Perhaps the most compelling evidence that eosinophilic esophagitis is a form of food allergy comes from the dramatic results of food elimination trials in children with the disorder. For example, Liacouras *et al.* reported that 98% of children with eosinophilic esophagitis who were treated with an elemental diet experienced both symptomatic and histological remissions (52).

The data presented above establish a plausible mechanism whereby PPI usage, by interfering with the peptic digestion of food allergens and by increasing mucosal permeability, might lead to the development of food allergy. The time course of the introduction and widespread usage of PPIs, especially in children, and the emergence of eosinophilic esophagitis, which appears to be a new form of food allergy, fits well with the hypothesis that PPIs may play an etiological role.

Problems with the hypothesis that PPIs contribute to the development of eosinophilic esophagitis

The mere demonstration of an association that has a plausible underlying mechanism does not establish cause and effect, and there are several potential problems with the hypothesis that PPIs contribute to the development of eosinophilic esophagitis. For example, some of the animal and human studies discussed above have linked PPIs with the development of IgE-mediated food allergy, but eosinophilic esophagitis does not appear to be an exclusively IgE-mediated allergic disorder (53). Indeed, it has been proposed that eosinophilic esophagitis may be primarily a cell-mediated, delayed hypersensitivity reaction to food allergens, which could explain why skin prick and other IgE-dependent tests often fail to identify the offending agents in patients with the disorder (54). Nevertheless, the development of food-specific IgE antibodies during PPI treatment is evidence that the use of those agents can result in food allergen-induced activation of the immune system, which conceivably could involve cell-mediated as well as IgE-mediated pathways. Conceptually, the mechanisms proposed to underlie

the development of PPI-induced food allergy (reduced peptic digestion of food allergens and increased gastric mucosal permeability) could contribute to cell-mediated as well as IgE-mediated immune responses.

Difficulties in determining precisely when eosinophilic esophagitis first appeared also cast some doubt on the etiological association with antisecretory medications. Although the first report that uses the term “eosinophilic esophagitis” was not published until 1978 (47), sometime after the introduction of cimetidine into clinical practice, there are case reports describing patients with esophageal stenoses typical of eosinophilic esophagitis that clearly predate the availability of any antisecretory agents (55). Furthermore, the use of antisecretory medications is now widespread, and yet eosinophilic esophagitis remains an uncommon disorder. These observations suggest that the use of acid-suppressive medications is neither a necessary nor a sufficient factor in the pathogenesis of eosinophilic esophagitis. It seems likely that the development of the disorder is a multifactorial process involving complex interactions among numerous environmental and genetic factors, all of which culminate in the exposure of a unique, genetically predisposed individual to environmental allergens that trigger the unusual immune response of eosinophilic esophagitis. The data discussed above summarize how antisecretory medications may facilitate that unique individual's exposure to critical antigens.

As with eosinophilic esophagitis, there appears to have been a substantial rise in the prevalence of food allergies, of extraintestinal allergic diseases (e.g., asthma, eczema), and of other eosinophilic gastrointestinal diseases over the past few decades (56,57). It is not clear whether acid-suppressive medications might also be contributing to the development of those disorders. The large majority of patients with eosinophilic esophagitis do not have eosinophilic gastroenteritis or clinical evidence of typical food allergies. A number of theories, which may pertain to eosinophilic esophagitis, have been proposed to explain the rising frequency of other allergic disorders, including the effects of increasing environmental pollution and global climate changes (58). One of the more interesting and plausible explanations involves the hygiene hypothesis, which holds that allergy develops in individuals who live in excessively hygienic environments as a consequence of their reduced encounters with infectious stressors (e.g., helminth infections) during early childhood (59,60). Authorities generally acknowledge that allergies develop through complex genetic and environmental interactions, and none of the competing theories mentioned above would exclude an additional contribution to the induction of allergy by antisecretory medications.

The complex relationship between GERD and eosinophilic esophagitis

One factor that will complicate attempts to establish a cause-and-effect link between PPIs and eosinophilic esophagitis is the disorder's complex relationship with GERD. Whereas both

GERD and eosinophilic esophagitis can be associated with esophageal eosinophils and both may cause symptoms such as heartburn and dysphagia, it can be difficult sometimes to distinguish between the two disorders (61). Children with eosinophilic esophagitis may be mistakenly diagnosed initially as having GERD and may be treated with PPIs (mistakenly prescribed to treat GERD) for years before the correct diagnosis is finally established. Alternatively, infants and young children who do not have either eosinophilic esophagitis or GERD, but who have nonspecific symptoms such as fussiness and dyspepsia, may be diagnosed empirically as having GERD and treated for protracted periods with potent antisecretory medications. It appears that PPIs are prescribed for children on the basis of clinical impression far more frequently than on the basis of formal testing for GERD. Finally, even if the initial diagnosis of GERD is correct, protracted PPI treatment of that chronic condition might contribute to the later development of eosinophilic esophagitis.

An epidemiological study seeking to establish an association between previous PPI usage and eosinophilic esophagitis is likely to suffer from the bias of confounding by indication. Furthermore, recent data indicate that the interaction between GERD and eosinophilic esophagitis can be complex, and that the notion of establishing a clear distinction between the two disorders is too simplistic (61). GERD may play a pathogenetic role in some patients with eosinophilic esophagitis and vice versa. PPI treatment has been shown to decrease esophageal eosinophilia dramatically in some patients with GERD (62). Consequently, a trial of PPI therapy is recommended as initial therapy for patients with eosinophilic esophagitis, even if the diagnosis seems clear-cut (61,63,64). Thus, it seems highly likely that many patients diagnosed with eosinophilic esophagitis will have been exposed to PPIs.

A first step in elucidating the relationship between antisecretory medications and eosinophilic esophagitis will be careful, epidemiological investigations that involve detailed questioning of patients and their parents regarding prior usage of the medications, especially in early childhood, and the specific indications for that usage. Special attention can be given to patients who had formal testing (e.g., esophageal pH monitoring) to establish a diagnosis of GERD before antisecretory medications were prescribed. The development of animal models in which esophageal eosinophilia is induced by food antigen exposure would be most helpful, but existing models that rely on aeroallergen exposure also might be tested for the effects of acid inhibition on esophageal eosinophil infiltration.

PPIs have been a mainstay of therapy for patients with GERD for almost two decades, and during that time they have established an excellent track record for safety. Despite the plausible mechanism discussed above, by no means is it clear that PPIs and other acid-suppressive medications have contributed to the rising frequency of eosinophilic esophagitis. Data directly linking PPIs with food allergy so far have come primarily from a single center in Vienna, and it would be reassuring to see those findings reproduced in other institutions. Nevertheless,

those investigators are to be congratulated for their intriguing and provocative studies. Clearly, the association between the use of antisecretory medications and eosinophilic esophagitis warrants further investigation.

CONFLICT OF INTEREST

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