Acid suppression therapy and allergic reactions

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Summary

The development of pharmaceutical agents such as sucralfate, histamine 2 (H2) receptor blockers and proton pump inhibitors (PPIs) reducing gastric acidity has been a mile stone for treatment of dyspeptic disorders. However, due to current prescription habits resulting in overuse of these potent drugs as well as over-the-counter (OTC) availability associated with self-medication, substantial health concern is related to the mechanisms of drug action as well as known side effects influencing gastrointestinal physiology.

More than a decade ago the first study appeared reporting an association between anti-ulcer drug intake and food allergy development. Ever since this first report several experimental as well as human studies verified this correlation, demonstrating that acid suppressive drugs not only influence the sensitization capacity of orally ingested proteins, but also represent a risk factor for food allergy patients. Additionally, gastric acid suppression was reported to increase the risk for development of drug hypersensitivity reactions. These consequences of anti-ulcer drug intake might on the one hand be associated with direct influence of these drugs on immune responses. On the other hand reduction of gastric acidity leads to impaired gastrointestinal protein degradation. Nevertheless, also disruption of the gastrointestinal barrier function, changes in microbiome or lack of tolerogenic peptic digests might contribute to the connection between anti-ulcer drug intake and allergic reaction. Therefore, these drugs should only be prescribed based on a precise gastroenterological diagnosis taking into consideration allergological mechanisms to ensure patients’ safety.

Keywords

gastric acid suppression medication; proton pump inhibitors; H2 receptor blockers; food allergy; drug allergy; sensitization

Introduction

Until the 1970s treatment of diseases associated with inadequate gastric acid secretion was limited to the use of antacids neutralizing excessive gastric acid and partial surgical elimination of the stomach. As this treatment was associated with insufficient mucosal
healing and as surgical interventions expectably had severe side effects, effective pharmacological control of gastric acid secretion was a desirable goal of pharmaceutical research. In 1972 the first H2 receptor blocker buimamide was developed. This major pharmaceutical break-through was followed by development of the widely prescribed H2 receptor antagonist cinetidine in 1975.[1] The major advantage of both compounds was the direct interference with the acid stimulating capacity of histamine via its receptor on parietal cells.

Only a few years later, first studies on the ulcer-healing and pepsin-binding properties of the basic aluminum sucrose sulfate complex termed sucralfate were published and this drug class was approved for the treatment of acute ulcers as well as continuous maintenance therapy for disease recurrence prevention.[2, 3]

In parallel pharmaceutical companies continued their efforts to develop novel therapeutics to reduce gastric acid output. In 1988 the PPI omeprazole was approved in Europe, which was followed by marketing of the same compound two years later in the US.[4] This and the other drugs with proton pump inhibitory action being subsequently released were quickly accepted as clinically superior to previous antisecretory medication.[5]

Besides their substantial benefit for management of patients with dyspeptic disorders gastric acid suppressive drugs can be considered a goldmine for the pharmaceutical industry. Even at the end of the patent protection period the PPI esomeprazole is still among the top selling drugs worldwide and the first PPI on the market omeprazole and esomeprazole were recently ranked among the all-time best selling drugs.[6, 7]

Besides an indicated long term use of this medication for relapse prevention in case of gastro-esophageal reflux (GERD), reflux esophagitis and non-erosive reflux disease (NERD) [8] there is substantial health and also economical concern about overuse and the inadequate prescription habits of acid suppression drugs. Several studies revealed that around 70% of patients admitted to nursing facilities or being hospitalized were on acid suppressive medication with more than 50% of them without an appropriate diagnosis justifying prescription.[9, 10] Another major health concern is the current inappropriate self-medication habit. Approximately 80% of patients with dyspeptic disorders of minor severity do not seek medical advice and simply use OTC available acid suppressive drugs.[11]

**Mechanisms of action and side effects of anti-ulcer drugs**

From a chemical point of view antacids are weak bases, such as hydroxides or carbonates, which are used to neutralize hydrochloric acid in the stomach.[12] They are formulated as salts of an alkaline ion in combination with one polyvalent cation such as calcium, aluminum and magnesium. Even though they are rarely prescribed by physicians, antacids are frequently used without prescription due to OTC availability. Major concerns regarding safety of these drugs are the observed pH dependent or chelation dependent drug interactions.[13]

Being a derivative of aluminum hydroxide containing antacids, sucralfate is a salt of sucrose sulfate and aluminum hydroxide. The drug was demonstrated to be activated in the presence
of acidity. Upon release of aluminum, the molecule obtains a negative charge interacting with positively charged chemical groups in its environment such as e.g. H\(^+\) ions, drugs or mucins. It is known for its pepsin binding capacity, thereby reducing pepsin concentration in gastric juices.[14, 15] Moreover, sucralfate has a mucosal protective effect by forming a physical barrier in the form of complex gels and interacts with high affinity with normal as well as inflamed mucosa.[16, 17, 18] In post-marketing evaluations sucralfate was described as an efficient and safe drug with limited side effects,[19, 20] with obstipation reported as the most common undesired effect occurring in up to 15% of patients.[16, 21]

As histamine has an acid secretion activation function via its H\(_2\) receptor on parietal cells, interference with this receptor by antagonists, was the first available causative treatment option for dyspeptic disorders. Later it was found that the acid secretion antagonizing effect of H\(_2\) receptor blockers is not only due to inhibition of histamine stimulation, but also due to interference with carbachol and gastrin stimulation which both act via H\(_2\) receptors.[22] Regarding side effects of these drugs the initial fear of many physicians was predisposition to bacterial overgrowth and consequently elevated intragastric levels of N-nitrosoamine, a known carcinogen. However, long-term clinical experience proofed these drugs not to harbor cancer inducing properties.[23] Regarding bacterial overgrowth and infections, these drugs seem to pose a minor risk compared to PPIs as reviewed below, probably due to the observed circadian changes in acid control by H\(_2\) receptor blockers.[22] Nevertheless, it is well accepted that H\(_2\) receptor blockers strongly interfere with cytochrome P450 (CPY450) enzymes, which requires special caution regarding interaction with other pharmaceuticals.[24]

PPIs were designed to acquire their potential acid suppressive function via specific and irreversible inhibition of the H\(^+\)K\(^+\)ATPase located in the secretory membrane of the parietal cells.[25, 26, 27] Influencing function and bioavailability different PPI subclasses revealed variations in speed and degree of gastric acid reduction but also in metabolism by hepatic CYP450 enzymes.[28] One side effect of PPIs and other acid-reducing drugs is the lowered bioavailability of drugs depending on acidic intragastric pH for absorption. PPIs may further alter the first pass metabolism and hepatic drug elimination.[29] PPIs are known to not only change intestinal bacterial composition [30] but also to be associated with intragastric bacterial overgrowth [31] which might lead to lung colonization and subsequently pneumonia by aspiration.[32] In general hospital settings but also in intensive care units (ICUs) gavage of PPI to critically ill patients for stress ulcer prophylaxis was associated with an increased risk for Clostridium difficile associated diarrhea.[33, 34] In contrast, PPIs might have an anti-microbial effect on some pathogens by blocking the proton pump in the membrane of certain bacteria and fungi.[35, 36] Furthermore, rare cases of anaphylactic reactions upon intake of omeprazole were reported in literature, with potential for crossreactivity between different PPI subclasses as indicated by intradermal skin testing.[37, 38]
The impact of acid reduction drugs on digestive capacity and function of the gastrointestinal tract

As indicated above acid-reduction medication either binds protons in the gastric lumen or substantially reduces the gastric acid output, which is the therapeutic goal for treatment of acid related disorders. Acidity itself is not only required for protection against infectious agents, but also initiates protein degradation by influencing food protein-food matrix and protein-protein interactions as well as structural properties of proteins. Additionally, acidity is a prerequisite for activation of the major gastric enzyme pepsin. Pepsin, produced by gastric chief cells, is secreted into the gastric lumen as the inactive proenzyme pepsinogen. Only at low intragastric pH levels the prosegment is released making the binding cleft available for protein interaction. As pepsin is the first protein degrading enzyme during gastrointestinal transit, interference with its function has major impact on protein digestion. Acidity of the chyme has a second main influence on gastrointestinal protein digestion. Upon arrival in the duodenum the acidic chyme represents the main stimulus for secretin release by S-cells mainly found in the duodenal mucosa (Fig. 1). Secretin is essential to stimulate pancreatic secretion of the proteases trypsin, chymotrypsin and carboxypeptidases. These proteases and peptidases are responsible for further peptide digestion into single amino acids or small peptides which are subsequently taken up by enterocytes for nutrition of the human body. Besides its influence on the gastric acidity, the PPI esomeprazole was even demonstrated to induce a significant transmucosal leak by compromising the barrier function of the upper gastrointestinal tract already after 5 days of medication. However, in patients with eosinophilic esophagitis (EoE) mucosal integrity of the esophagus was restored after high-dose treatment with PPIs in tissue samples from patients with PPI-responsive eosinophilia (PPI-REE). Thus, additional studies are needed to evaluate whether anti-ulcer drug intake might be associated not only with compromised digestive capacity of the gastrointestinal tract, but also with a leaky barrier function of the gastrointestinal tract with major implications on health and disease.

The influence of acid-suppression medication on the immune response

Already during the first years after approval for clinical practice studies appeared that suggested an influence of sucralfate on the immune response. Sucralfate was reported to activate the mucosal cyclooxygenase directly affecting the arachidonic acid metabolism and leading to elevated synthesis and release of leukotriene C4. Moreover, an enhanced production of prostaglandins from the gastric mucosa and activation of macrophages were described. Additionally, sucralfate, but also simple antacids are aluminum containing drugs, which might per se exert a substantial influence on the immune response. Despite common knowledge the first focused study evaluating the impact of the aluminum containing drug sucralfate on the immune response appeared in 2007. The authors revealed a Th2 shift after systemic application in an experimental model and speculated on a possible impact of aluminum on the observed immune response deviation.

The biogenic amine histamine exerts an effect in a large variety of different cells including important immune cells via its 4 receptors. Out of these 4 the H2 receptor is not only
expressed on gastric parietal cells, but additionally also on brain tissue, cardiac tissue, smooth muscle cells, T- and B-cells and dendritic cells.[52] Especially for dendritic cells histamine interaction via its H2 receptor was proposed to alter response to microbial ligands and promote T regulatory cells.[51, 53] Furthermore, it was proposed that H2 receptor activation might shift the immune response towards Th2 dominance. Thus, it is not surprising that H2 receptor antagonists have an eminent effect on the immune response with an overall immune-activating potential as reviewed by Biwas and colleagues.[54] In context with these above mentioned findings, it is of special interest that usage of H2 receptor antagonists in inflammatory bowel disease patients were reported to increase the risk for hospitalization.[55]

Also for PPI a reasonable number of studies report a direct influence on the immune response unrelated to the inhibition of gastric acid. PPIs were shown to have anti-oxidative effects in vitro and in vivo.[56, 57] As PPIs interfere with the proton pump, effects on other, non-gastric cells expressing the H⁺K⁺ATPase on extracellular membranes and intracellular organelles like neutrophils and endothelial cells can be expected.[58] It is known that PPIs decrease expression of intercellular adhesion molecules leading to reduced neutrophil accumulation as well as to inhibited oxidative burst of human neutrophils.[59] Additionally, PPIs were demonstrated to inhibit lysosomal enzymes with broad implication in infectious as well as tumor immune defense.[60] In contrast other studies even proposed an association between the intake of PPIs and decreased tumorigenesis, which in some of the studies was beyond the mucosa healing effect of the drugs.[61, 62] Furthermore, Lansoprazole treatment was described to down-regulate Th1 and Th2 signaling pathways in the human gastric mucosa [63] and to be associated with decreased levels of proinflammatory cytokines such as IL-6, IL-8 and TNF-α in cultured tracheal epithelial cells.[64] Interestingly, PPIs were also reported to inhibit IL-4 and IL-13 signaling via STAT6 [65] and in PPI-REE a marked reduction of eotaxin-3, IL-13, IL-5 mRNA expression was observed after PPI treatment.[66]

**The association of anti-ulcer drug intake and allergic reactions**

Based on the above reviewed data it is tempting to speculate that acid-reduction medication might also have an important influence on the allergic immune response. However, the first definitive indication of a correlation between anti-ulcer drug intake and food allergy development was the case history of a patient diagnosed with caviar allergy at our institution.[67] He reported to have been on acid-reduction medication during the first symptom-free consumption of Beluga caviar. Two years later he developed severe clinical symptoms including anaphylaxis at the second ingestion of caviar. Based on this knowledge we performed experimental studies confirming the correlation of gastric acid-reduction by anti-ulcer drug intake and the development of food allergy irrespective of the type of medication used (i.e. sucralfate, H2-receptor blockers or PPIs).[68, 69] The influence on IgE induction and skewing the immune response towards Th2 was confirmed for another subclass of H2-receptor blockers.[70] Furthermore, also less potent acid reduction medication, such as antacids and base powder, were found to be associated with food allergy development.[71] These results were confirmed in human studies evaluating the influence of long-term anti-ulcer drug intake on food sensitization and allergy induction. A cohort of 152 adult patients treated for dyspeptic disorder with either H2-receptor blockers or PPIs was
subjected to an allergological screening before and after a 3 month course of acid-reduction treatment. In these patients we observed a boost of preexisting food-specific IgE antibodies in 10% or de novo IgE formation towards regular constituents of the daily diet in 15% of all patients. Even though food specific IgE levels decreased in some patients 5 months after discontinuation of anti-ulcer medication intake, sensitization was still confirmed by positive skin tests.[72] Additionally, food allergy was diagnosed in a patients’ subgroup developing hazelnut specific IgE antibodies during anti-ulcer treatment by double-blind, placebo-controlled food challenges.[68] This correlation is not only of importance for adult patients but also for other age groups. Already during pregnancy intake of acid-suppression medication represents a risk for maternal food allergy development, but also shifts the immune response of the off-springs towards Th2 in an experimental model.[73] These results were underlined by a population-based birth register study revealing a link between maternal acid suppression therapy during pregnancy and the development of childhood asthma.[74] In line with these data intake of acid-suppression medication during childhood was suggested to be associated with an increasing prevalence of food allergy,[75, 76] However, also during immunosenescence in elderly patients gastric acid reduction is a risk for food allergy as indicated by experimental as well as human studies.[77, 78] Moreover, clinical studies revealed impairment of gastric digestion by gastric pH elevation to represent a causative factor for allergic reactions at lower amounts of ingested allergens in already food allergic patients.[79, 80] Not only for food allergy acid-suppression medication seems to be risk factor. We additionally reported a correlation between gastric acid suppression and development of IgE mediated hypersensitivity towards diclofenac.[81] In line with these findings, a retrospective chart review study reported PPI intake to increase the risk for the development of drug hypersensitivity reactions (DHR).[82] From this study no conclusion is possible on the influence of route of drug administration and drug metabolism on DHR induction during PPI treatment.

Of interest, in a subgroup of patients with EoE, a chronic immune-mediated disorder of the esophagus associated with eosinophilic infiltrates as well as eotaxin and Th2 cytokine overexpression, a therapeutic role to PPIs is increasingly accepted.[83] Even though mechanisms are not fully understood and therapeutic applications are controversially discussed,[84] an inhibitory action of PPI on eotaxin 3 expression by blocking STAT6 promotor binding in esophageal cells from patients with EoE was reported.[85] For a better mechanistic understanding, it is of special interest to investigate pathophysiological similarities and differences between PPI-REE and EoE as well as other Th2 driven diseases.

Discussion of causal relation between gastric acid reduction and allergy development

The connection between gastric acid reduction and allergy development can be seen in association with several mechanisms of actions or side-effects of these potent drugs.

First of all, acid-suppression medication substantially interferes with the digestive function of the gastrointestinal tract. A recent study in morbid obese patients undergoing bariatric
surgery underlined the important gate-keeping function of gastric digestion in allergy development. The patients’ sensitization profiles substantially changed after elimination of adequate digestion by gastric bypass surgery.[86] Moreover, at least for food allergy induction resistance of food proteins to gastric digestive enzymes seems to be decisive for allergenicity and has for a long time been regarded as predictive for their sensitizing capacity.[41] Digestion experiments with simulated gastric fluid were even considered to distinguish between potentially allergenic and non-allergenic food compounds and digestion labile food proteins were termed non-sensitizing elicitors.[87, 88] However, during the past decades it has become evident that major food allergens inducing allergic sensitization via the oral route are readily degraded by gastric enzymes under physiological conditions.[89] Especially for these food proteins interference with the gastrointestinal digestion as it is the case under acid-reduction medication, might have major consequences increasing the risk for food allergy development.[41]

Moreover, gastric digestion itself is considered to contribute to tolerance induction via the oral route. The concept of tolerogenic properties of peptic fragments of food proteins goes back to the late 1970ies. At that time first studies reported peptic fragments of the model allergen bovine serum albumin (BSA) to be capable of suppressing an antibody response in immunization experiments due to T-cell interaction.[90, 91] Pepsin and trypsin digest of certain food allergens might still have retained immunogenic properties of fragments especially with regards to T-cell activation.[92, 93] Furthermore, digestion-resistant food proteins might even have an intact IgE binding capacity after pepsin incubation.[94] Based on this knowledge experimental trials evaluated pepsinized food protein digests for the development of novel therapeutic approaches in food allergy and demonstrated beneficial effects on cashew nut and cow’s milk allergy.[95, 96] Thus, hindrance of gastric digestion under anti-ulcer medication might not only increase the sensitization capacity of food proteins by leaving them undigested but additionally might reduce the availability of tolerogenic digestion fragments.

Another risk factor for allergy induction under acid reduction medication might be its interference with epithelial barrier function. The integrity of the gastrointestinal epithelium gains increasing attention as dysfunction of the intestinal epithelial barrier is currently discussed as a contributing factor in development and progression of various diseases including food allergy.[97, 98] Interestingly, high levels of total and food-specific IgE were measured in the gastrointestinal mucosa of peptic ulcer patients which was discussed as a result of enhanced mucosal permeability in H. pylori infection.[99, 100] Also for other diseases of the upper gastrointestinal tract such as Barrett’s esophagus an increased transepithelial leak was described.[101] In 2008 a first report appeared linking PPI intake with increased transmucosal leak in the upper gastrointestinal tract.[44] However, in patients with PPI-REE integrity of the esophageal mucosa was restored after PPI treatment. Due to the different outcome in these studies and due to the lack of information on the influence of acid suppressive drugs on barrier function of other parts of the gastrointestinal tract, further studies are needed to evaluate a possible contribution to allergy development. Last but not least acid suppression drug might influence the gastrointestinal microbiome. Gastric acid reduction is known to change the intestinal microbial composition.[102] On the one hand PPIs substantially increase the number of bacteria in the oral cavity and the upper
gastrointestinal tract due to lack of gastric acidity. One the other hand PPIs might have an anti-microbial effect on certain microbes by inhibiting the H^+K^+ATPase found in bacterial and fungal cell membranes. Microbiome changes during anti-ulcer drug treatment and the known influence of the intestinal bacterial composition on food allergy could offer a further mechanistic explanation for the observed association between pharmaceutical gastric acid-suppression and allergy development. Without any doubt additional research is needed to in-depth evaluate this possible interaction.

**Conclusions and clinical out-look**

The functional homeostasis of the gastrointestinal tract is essential for overall immunological health and allergy prevention. Even though treatment with anti-ulcer drugs has an essential health benefit for patients with acid related disorders and is increasingly recognized for treatment of a subset of patients with EoE, it has to be taken into consideration that acid suppression medication substantially interferes with the physiological properties of the gastrointestinal tract. Several mechanisms of action or side effects of these potent drugs could beneficially or detrimentally influence ongoing immune responses. So far experimental as well as clinical studies outlined an association between gastric acid suppression and allergy induction. The causative factors for this correlation probably go beyond the influence of acid reduction medication on gastrointestinal protein digestion and might explain the observed variations between patients regarding allergy induction. Therefore, prescription of this medication should be based on a clear gastroenterological diagnosis with avoidance of long-term intake, if possible. Additionally, it seems to be crucial to consider the immunological impact of these drugs to ensure full therapeutic benefit and patients’ safety. Additional mechanistic studies as well as extensive interdisciplinary exchange are clearly needed and will be essential in the future.

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**References**


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Figure 1. Mechanisms of action of acid suppression medication. While antacids and sucralfate directly bind protons in the gastric lumen, other drugs interfere with the gastric acid production of parietal cells. H2 receptor antagonists block the activating function of histamine via its H2 receptor. PPIs irreversibly inhibit the proton pump in the secretory cell membrane of parietal cells. The resulting elevated gastric pH leads to reduced pepsin activation in the stomach as well as duodenal secretin release, which substantially interferes with the gastrointestinal protein digestion.