

Histamine 2 Receptor Antagonists and Proton Pump Inhibitors

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Within the last 50 years, the pharmacologic market for gastric disease has grown exponentially. Currently, medical management with histamine 2 receptor antagonist and proton pump inhibitors are the mainstay of therapy over surgical intervention. These are generally regarded as safe medications, but there are growing numbers of cases documenting adverse effects, especially those manifesting in the skin. Here we review the pharmacology, common clinical applications, and adverse reactions of both histamine 2 receptor antagonists and proton pump inhibitors with a particular focus on the potential for allergic reactions including allergic contact dermatitis.

Within the last 50 years, the pharmacologic market for gastric disease has grown exponentially. Before the introduction of histamine 2 receptor antagonists (H₂RAs), very little was available outside of acid neutralization compounds and anticholinergics. Surgery was considered the mainstay of therapy. Yet, with the development of H₂RAs in the 1970s and proton pump inhibitors (PPIs) in the 1980s, pharmacologic therapy quickly became the mainstay of treatment.^{1,2} While each has a favorable safety profile, there are growing numbers of cases documenting adverse effects, especially those manifesting in the skin. These medications are both frequently prescribed and widely available without a prescription as over-the-counter (OTC) formulations. Therefore, it can be important to consider these medications in the differential diagnosis of new or refractory skin disease.

HISTAMINE 2 RECEPTOR ANTAGONIST

Histamine 2 receptor antagonists were the breakthrough class of pharmaceuticals developed for the treatment of hyperacidity and the first shown to reduce acid production. Sir James W. Black of Smith, Kline & French spearheaded the program for development and successfully synthesized cimetidine in 1972. This was the first H₂RA released to market in 1976.³ However, a multitude of drug interactions and adverse effects, including reports of cutaneous

delayed hypersensitivity reactions, were noted.⁴ This led to the subsequent development of ranitidine, famotidine, and nizatidine. Table 1 highlights the available H₂RAs, available formulations, and potential additives that should be considered when presented with an adverse drug reaction.⁵

Chemical Structure

The backbone structure of this group is based on histamine. The general structure includes 3 bioactive fragments: (1) substituted heteroaromatic ring, (2) thioether side chain, and (3) neutral polar moiety constituted by a HN=C=NH system.⁶ Cimetidine contains an imidazole ring and cyanoguanidine group.⁷ Ranitidine was created by the substitution of a furan for the imidazole ring. Famotidine and nizatidine were created by substitution of a thiazole for the imidazole group.⁸ Famotidine is structurally distinct from nizatidine because of a guanidyl substituent on the thiazol ring that allows for hydrogen bonding within the molecule and the polar moiety has an amidine group in place of guanidine.⁶ While there is a paucity of literature regarding potential cross-reactivity between these agents, reports of patients who have been patch tested to multiple H₂RAs suggest that cross-reactivity is uncommon.⁹

Mechanism of Action

The H₂RAs are competitive inhibitors of the histamine 2 receptor on the surface of parietal cells. Once bound, H₂RAs block activation of adenylate cyclase thereby preventing increased intracellular cyclic adenosine monophosphate and activation of protein kinase A. Protein kinase A normally activates cytoskeletal proteins involved in transport of the H⁺/K⁺ adenosine triphosphatase (H⁺/K⁺ ATPase) from cytoplasm to plasma membrane. The blockade is 2-fold as it directly blocks stimulation by histamine but also diminishes the effect of direct parietal cell stimulation by gastrin and

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TABLE 1. Histamine 2 Receptor Antagonists

Generic Name	Brand Name	Potential Additives
Cimetidine	Tagamet (tablet, liquid, injection, IV)	Tablets 300 mg, 400 mg, or 800 mg: cellulose, D&C yellow no. 10, FD&C blue no. 2, FD&C red no. 40, FD&C yellow no. 6, hydroxypropyl methyl cellulose, iron oxides, magnesium stearate, povidone, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide Liquid 300 mg/5 mL: FD&C yellow no. 6, flavors, methylparaben, polyoxyethylene polyoxypropylene glycol, propylene glycol, propylparaben, saccharin sodium, sodium chloride, sodium phosphate, sorbitol, and water Injection: phenol IV: phenol
Ranitidine	Zantac (tablet, Rdose tablet, syrup, injection)	Tablets 150 mg or 300 mg: Zantac 150—FD&C yellow no. 6 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide; Zantac 300—croscarmellose sodium, D&C yellow no. 10 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin Rdose Tablets 25 mg: aspartame, monosodium citrate anhydrous, povidone, sodium bicarbonate, sodium benzoate Syrup 15 mg/1 mL: alcohol, butylparaben, dibasic sodium phosphate, hypromellose, peppermint flavor, monobasic potassium phosphate, propylparaben, purified water, saccharin sodium, sodium chloride, and sorbitol Injection: phenol, monobasic potassium phosphate, dibasic sodium phosphate
Famotidine	Pepcid (tablet, oral suspension)	Tablet 20 mg or 40 mg: hydroxypropyl cellulose, hypromellose, iron oxides, magnesium stearate, microcrystalline cellulose, corn starch, talc, titanium dioxide, and carnauba wax Oral suspension 40 mg/5 mL: anhydrous citric acid, flavors (cherry, banana, and mint), microcrystalline cellulose and carboxymethyl cellulose sodium, confectioner's sugar, corn starch, colloidal silicon dioxide and xanthan gum, sodium benzoate, sodium methylparaben
Nizatidine	Axid (capsule, oral solution)	Capsule 150 mg or 300 mg: gelatin, pregelatinized starch, dimethicone, starch, titanium dioxide, yellow iron oxide, magnesium stearate, croscarmellose sodium, povidone, red iron oxide, and talc Oral solution 15 mg/1 mL: methylparaben, propylparaben, glycerin, sodium alginate, purified water, sodium chloride, saccharin sodium, sodium citrate dihydrate, citric acid anhydrous, sucrose, bubble gum flavor, artificial sweetness enhancer, and sodium hydroxide

Currently marketed H₂RA and their potential additives.

acetylcholine. They most effectively suppress basal secretion, which is stimulated by histamine release, but they also have a mild effect on meal-stimulated acid production due to its strong stimulation by gastrin and acetylcholine.¹⁰

Pharmacokinetics and Pharmacodynamics

The mean half-life is 1 to 4 hours, and each drug is eliminated via a mixture of hepatic metabolism through the cytochrome P450 system (CP450) and renal excretion through glomerular filtration and tubular secretion.⁸ Cimetidine, ranitidine, and famotidine undergo first-pass hepatic metabolism. Conversely, nizatidine undergoes very little first-pass metabolism. Because these molecules are competitive inhibitors, potency is vitally important. The most potent is famotidine at 20 to 50 times that of cimetidine. Ranitidine is the least potent at 6 to 10 times less than cimetidine. The collective group bioavailability is 50% to 70%.¹¹

Clinical Use

In the past, these molecules were the most widely used to treat gastroesophageal reflux disease (GERD), peptic ulcer disease, nonulcer dyspepsia, and prevention of bleeding from stress-related gastritis. More recently, these roles have been filled by the newer PPIs. H₂RAs are still used today, both in OTC and prescription form, for intermittent and chronic treatment of GERD. For uncomplicated ulcers not caused by *Helicobacter pylori*, H₂RAs still have some role and can result in healing rates of 80% to 90% after 6 to 8 weeks of nocturnal therapy.¹⁰ Lastly, for bleeding prevention in critically ill patients, H₂RAs are used to raise intragastric pH. However, studies have failed to show which agent, PPIs or H₂RAs, is superior.¹⁰

Renewed interest has been seen in off-label use of H₂RAs in the treatment of some commonly encountered dermatologic conditions. Specifically, cimetidine has been tried with mixed

results to treat verruca¹² and epidermodysplasia verruciformis,¹³ whereas ranitidine is often employed in the management of urticaria.¹⁴ Cimetidine may also have a role in treatment and prophylaxis of acute attacks of acute intermittent porphyria,^{15,16} porphyria cutanea tarda,^{17,18} and erythropoietic protoporphyria¹⁹ through hepatic enzyme modulation. It can be used in patients on high-dose dapsone therapy to decrease the risk of hematologic adverse events.²⁰ Anecdotal case reports can be found where cimetidine was used in the management of herpes zoster,^{21,22} erythema multiforme,²³ and psoriasis.²⁴ These applications have not been widely adapted into clinical practice. Interestingly, ranitidine has been investigated in the treatment of hand eczema. Veien et al²⁵ found that when used as an adjuvant to topical steroids, ranitidine was more effective at reducing the area of involvement as compared with placebo, but other measures such as erythema, scaling, and vesicle number were not statistically significant. Its use in psoriasis has also been investigated. Kristensen et al²⁶ found that daily ranitidine significantly decreased the Psoriasis Area Severity Index score in their patients after 3 to 6 months of therapy.

Adverse Dermatologic Reactions

Of the H₂RAs, ranitidine is the most documented compound causing adverse dermatologic reactions. There are reports of ranitidine causing urticaria and angioedema^{27,28}; however, anaphylactic reactions are extremely rare. Type III hypersensitivity reactions such as small vessel vasculitis have been reported.^{29–31} Type IV hypersensitivity reactions have been reported primarily in occupational settings. The Bureau of Labor Statistics estimated an annual incidence rate for occupational skin disease of 46 cases per 100,000 workers in 2000.³² It has been estimated that 4% of all documented occupational dermatitis cases occur in the health care or pharmaceutical industry.³³ Gielen and Goossens³⁴ investigated occupational allergic contact dermatitis (ACD) from drugs in health care workers and found antibiotics to be the most common causative pharmaceutical agents. Interestingly, 11.4% of their patients were positive to ranitidine. Other reports found in the literature of ACD to ranitidine include exposure to a veterinary product,³⁵ occupational exposure during manufacturing,^{36,37} nonoccupational exposure during crushing of ranitidine tablets,³⁸ and oral ingestion.³⁹ Allergic contact dermatitis has also been reported with cistoran, an intermediate compound in ranitidine synthesis.⁴⁰ Similar cases to intermediate compounds have been reported in the synthesis of famotidine.⁴¹

The prototypical presentation for occupational ACD to H₂RAs is dermatitis localized to an airborne distribution. This distribution includes involvement of the face, upper eyelids, postauricular skin, neck, upper chest, dorsal forearms, and dorsal hands. While a photodistributed pattern is similar, the upper eyelids and postauricular skin are typically spared. Wiszniewska and Walusiak-Skorupa⁴² name pharmaceuticals as one of the most common causes of airborne contact dermatitis in their 2015 review of occupational contact dermatitis, highlighting the importance of recognizing this diagnosis.

Other rare cutaneous reactions with H₂RAs have included acute generalized exanthematous pustulosis (AGEP),^{43–45} UVB photosensitivity,⁴⁶ pseudochromhidrosis,⁴⁷ and symmetrical drug-related intertriginous and flexural exanthema.⁴⁸ Table 2 summarizes these cases and their causative agent.

PROTON PUMP INHIBITORS

The original molecule, timoprazole, was developed by the pharmaceutical company Hässle. However, due to negative effects on the thyroid and thymus glands, this was never released to market. The timoprazole derivative, omeprazole, was discovered in 1979 and approved for sale in Europe in 1988 and the United States in 1990.² Now, multiple medications within this class have been developed and include lansoprazole, rabeprazole, pantoprazole, and esomeprazole. Table 3 highlights commonly used PPIs, available formulations, and potential additives.⁵

Chemical Structure

Proton pump inhibitors all share a basic structure with a substituted pyridine linked to different benzimidazoles. They are weak bases with a pK_a1 between 3.8 and 4.9, which allows for accumulation in the acidic environment around the secretory portion of the parietal cell. The specific PPIs are differentiated by their substituents on the pyridine or benzimidazole ring; omeprazole, esomeprazole, and pantoprazole have substitutions on the benzimidazole ring but rabeprazole and lansoprazole do not. These small differences allow them to bind to different cysteines on the H⁺/K⁺ ATPase.⁴⁹ It is the difference of binding site that modifies biological activity. Cross-reactivity among PPIs has been reported.^{50,51}

Mechanism of Action

Proton pump inhibitors are defined as acid-suppressive agents that work by blocking release of acid from parietal cells by inhibiting H⁺/K⁺ ATPase. They are the most effective acid blocking medication on the market given their ability to inhibit production from all 3 sources of stimuli (acetylcholine, gastrin, and histamine).⁵² The acidic environment allows for conversion of the prodrug to its active form, a sulphenamide, through a proton-catalyzed process. A covalent bond is formed between the sulphenamide and cysteine residues of H⁺/K⁺ ATPase leading to its inhibition.⁵³

Pharmacokinetics and Pharmacodynamics

The average half-life of all currently marketed PPIs in blood is 1 hour. However, once bound to H⁺/K⁺ ATPase, they inhibit acid secretion for the half-life of the pump enzyme (approximately 48 hours). As a result, only 70% of the pump enzymes are bound and inhibited.⁴⁹ The only PPI to have a longer half-life, approximately 9 hours, is tenatoprazole. It has an imidazopyridine group instead of benzimidazole, which slows metabolism. However, this molecule has been slow to pass through clinical trials and as of

May 2015 was still in phase 1.⁵⁴ They are all metabolized by the liver via the cytochrome P₄₅₀ system. Each drug has slightly different metabolism, which leads to unique drug interactions within this system.⁵⁵

The oral bioavailability of the PPIs as a group is high. Omeprazole is unique in that it varies with repeat dosing, ranging from 36% after first dose to 60% with repeat dosing. Esomeprazole also varies with repeat dosing from 64% at first dose to 89% with repeat dosing.⁵⁶ The others do not vary with dosing: lansoprazole 80%, rabeprazole 52%, and pantoprazole 77%.^{55,57,58}

Clinical Use

Today, these are the most effective and widely prescribed medication for gastric disease, including reflux esophagitis, duodenal and gastric ulcers, and Zollinger-Ellison syndrome. A meta-analysis completed by Caro et al⁵⁹ demonstrated similar efficacy of the newer PPIs compared with omeprazole in acute heartburn control, healing rates, and relapse rates. The only molecule not included in their study was esomeprazole, which was found to have increased efficacy and reduced patient variability compared with omeprazole.⁵⁶

The most common dermatologic use of PPIs is as a prophylactic agent against peptic ulcer formation in those on long-term corticosteroid therapy. However, there is some debate as to whether it is medically necessary given the low risk of peptic ulcers in those on corticosteroids. Dorlo et al⁶⁰ found that less than 2% of those on corticosteroids develop peptic ulcers and felt that there was no indication for PPI prophylaxis in patients on

corticosteroids alone. However, they did note that those on concurrent treatment with corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) should receive PPI prophylaxis.

Another dermatologic indication for PPIs is in the management of systemic scleroderma with gastrointestinal involvement. It is estimated that 60% to 90% of systemic scleroderma patients have reflux esophagitis. The extent of cutaneous disease is a poor marker for gastrointestinal involvement. Studies have shown that 50% to 60% of patients with only limited cutaneous involvement have reflux disease.⁶¹ These patients also have a higher rate of gastritis. Patients with systemic scleroderma are also often managed with concomitant NSAIDs. It is prudent to consider gastrointestinal involvement and evaluate for *H. pylori* presence if indicated in patients with systemic scleroderma. *Helicobacter pylori* infection should be adequately treated with first-line therapy, and in those with concurrent NSAID use, prophylaxis with a PPI is indicated.⁶² In those with reflux esophagitis, treatment should include PPI; rabeprazole 10 mg daily was effective in 1 study.⁶¹

In the last 20 years, *H. pylori* has been hypothesized to play a role in dermatologic diseases such as rosacea,^{63,64} atopic dermatitis,⁶⁵ chronic idiopathic urticaria,⁶⁶ immune thrombocytopenic purpura,⁶⁷ nummular dermatitis, pruritus cutaneous, and prurigo.⁶⁸ A study by Sakurane et al⁶⁹ indicated that underlying chronic *H. pylori* infection may be a trigger for cutaneous disease, and it may result in disease refractory to conventional therapy. Several case reports and larger studies have also suggested that treatment of *H. pylori* can result in partial or complete resolution of skin disease.^{65,66,70,71} The recommended treatment for *H. pylori*

TABLE 2. Adverse Cutaneous Reactions to H₂RAs

Author	Clinical Manifestation	H ₂ RA
Picardo and Santucci ²⁷	Facial edema, urticaria, 1 case	Ranitidine
Song et al ²⁸	Urticaria, anaphylaxis, 2 cases	Ranitidine
Mitchell et al ²⁹	Small vessel vasculitis, 1 case	Cimetidine
Andreo et al ³⁰	Small vessel vasculitis, 1 case	Famotidine
Suh et al ³¹	Small vessel vasculitis, 1 case	Nizatidine
Meani and Nixon ³⁵	Allergic contact dermatitis, 1 case	Ulcerguard*
Ryan et al ³⁶	Allergic contact dermatitis, 7 cases	Ranitidine, ranitidine base
Romaguera et al ³⁷	Allergic contact dermatitis, 16 cases	Ranitidine base
Mendieta Eckert et al ³⁸	Allergic contact dermatitis, 1 case	Ranitidine
Juste et al ³⁹	Allergic contact dermatitis, 1 case	Ranitidine
Valsecchi et al ⁴⁰	Allergic contact dermatitis, 2 cases	Ranitidine chemical pathway intermediate, Cistoran
Guimaraens et al ⁴¹	Allergic contact dermatitis, 3 cases	Famotidine
Montersetrin and Conde ⁹	Allergic contact dermatitis, 1 case	Famotidine
Peters ⁴	Allergic contact dermatitis, 1 case	Cimetidine
Hausermann et al ⁴⁸	SDRIFE	Cimetidine
Blanes Martinez et al ⁴³	Acute generalized exanthematous pustulosis, 1 case	Ranitidine
Sawhney et al ⁴⁴	Acute generalized exanthematous pustulosis, 1 case	Ranitidine
Burrows and Russell Jones ⁴⁵	Acute generalized exanthematous pustulosis, 1 case	Cimetidine
Kondo et al ⁴⁶	UVB photosensitivity	Ranitidine
Hill et al ⁴⁷	Pseudochromhidrosis	Ranitidine

Adverse clinical reactions documented in the literature to various H₂RAs.

*Ulcerguard is a veterinarian injection used in horses. It contains 19% ranitidine.

SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

TABLE 3. Proton Pump Inhibitors

Generic Name	Brand Name	Potential Additives
Omeprazole	Prilosec (capsule, oral suspension)	Delayed release capsule (10 mg, 20 mg, 40 mg): cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hypromellose, lactose, mannitol, sodium lauryl sulfate, gelatin-NF, FD&C blue no. 1, FD&C red no. 40, D&C red no. 28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C blue no. 2, D&C red no. 7 calcium lake, D&C yellow no. 10 (10 mg and 40 mg) Oral suspension 2.5 mg or 10 mg: glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer C, polysorbate, sugar spheres, talc, and triethyl citrate, citric acid, crospovidone, dextrose, hydroxypropyl cellulose, iron oxide, and xanthan gum
Lansoprazole	Prevacid (capsule, SoluTab, IV)	Delayed release capsule 15 mg or 30 mg: sugar sphere, sucrose, methacrylic acid copolymer, low substituted hydroxypropyl cellulose, starch, magnesium carbonate, talc, polyethylene glycol, titanium dioxide, polysorbate 80, hydroxypropyl cellulose, colloidal silicon dioxide, D&C red no. 28, FD&C blue no. 1, FD&C green no. 3, and FD&C red no. 40 SoluTab 15 mg or 30 mg: mannitol, methacrylic acid, hydroxypropyl cellulose, lactose monohydrate microcrystalline cellulose sphere, triethyl citrate, crospovidone, polyacrylate, magnesium carbonate, aspartame, glyceryl monostearate, hypromellose, magnesium stearate, citric acid, titanium dioxide, talc, artificial strawberry flavor, polyethylene glycol, polysorbate 80, and ferric oxide IV: mannitol, meglumine, and sodium hydroxide
Rabeprazole	Aciphex (tablet, Sprinkles)	Tablet 20 mg: carnauba wax, crospovidone, diacetylated monoglycerides, ethyl cellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, propylene glycol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, iron oxide yellow, iron oxide red Sprinkles 5 mg or 10 mg: colloidal silicon dioxide, diacetylated monoglycerides, ethyl cellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium oxide, magnesium stearate, mannitol, talc, titanium dioxide, carrageenan, potassium chloride, FD&C blue no. 2 aluminum lake (in the 5 mg capsule), FD&C yellow no. 6 (in the 10 mg capsule), and gray printing ink
Pantoprazole	Protonix (tablet, oral suspension)	Tablet 20 mg or 40 mg: calcium stearate, crospovidone, hypromellose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate Oral suspension 40 mg: crospovidone, hypromellose, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide
Esomeprazole	Nexium (capsule, oral suspension, IV)	Capsule 20 mg or 40 mg: glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, triethyl citrate, gelatin, FD&C blue no. 1, FD&C red no. 40, D&C red no. 28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, <i>N</i> -butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C yellow no. 10 Oral suspension 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg: dextrose, xanthan gum, crospovidone, citric acid, iron oxide, and hydroxypropyl cellulose IV 20 mg or 40 mg: edetate disodium and sodium hydroxide (pH buffers)

Currently marketed PPIs and their potential additives.

includes any of the PPIs in combination with 2 antibiotics, most often amoxicillin and clarithromycin given for 7 to 14 days.

Adverse Dermatologic Reactions

In general, these medications are considered to be very safe. Proton pump inhibitors have reported adverse events in approximately 5% of patients, most commonly causing gastrointestinal upset, diarrhea, vomiting, and headache. The majority of adverse

dermatologic reactions have been hypersensitivity reactions. Omeprazole has been the most frequently implicated agent followed by lansoprazole, pantoprazole, esomeprazole, and rabeprazole.⁷² Numerous cases of isolated urticaria or urticaria in conjunction with other symptoms including dyspnea, swelling, and pruritus have been reported.^{51,72–74} In addition, angioedema has been observed in conjunction with urticaria alone⁵¹ and with symptoms including whole-body urticaria, pruritus, or dyspnea.^{74,75} Anaphylactic

reactions are rare but have been documented in 42 cases, according to the World Health Organization.

Delayed hypersensitivity reactions have been rarely reported accounting for an estimated 0.5% of adverse reactions to PPIs. However, as seen with H₂RAs, most are encountered in the occupational setting presenting with an airborne distributed dermatitis. Reports have included ACD in exposure to a veterinarian product containing omeprazole^{76,77} and exposure during manufacturing of omeprazole,^{78,79} lansoprazole,⁸⁰ and pantoprazole.⁸¹ Figure 1 illustrates a case of airborne ACD in a manufacturing plant employee. Figure 2 illustrates this patient's 2+ positive patch test reactions at 96 hours to omeprazole and pantoprazole. His facial dermatitis resolved with proper use of personal protective equipment. Table 4 summarizes other reported cutaneous reactions to PPIs. In addition, there have been 4 airborne cases of photoallergic dermatitis documented to omeprazole, rabeprazole, pantoprazole, and esomeprazole.¹⁰⁰

Other reactions including small vessel vasculitis,⁸² subacute cutaneous lupus,^{83–88} discoid lupus,⁸⁹ fixed drug eruption,^{90–92} AGEF,^{93,94} toxic epidermal necrolysis,^{95,96} Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome,^{97,98} Sweet syndrome,⁹⁹ and nonspecific bullous reactions¹⁰¹ have been documented with PPIs. Table 4 summarizes these cases and their causative agent.

MANAGEMENT OF REACTIONS

Diagnostic testing largely depends on the type of reaction. Type I hypersensitivity reactions may be diagnosed through skin and oral provocation testing (OPT). Often the most practical approach is to discontinue the suspected agent and monitor for skin clearance.



Figure 1. Patchy persistent dermatitis on the face, postauricular scalp, dorsal hands, and forearms consistent with airborne contact dermatitis.



Figure 2. The superior patch reaction is a 2+ positive reaction at 96 hours to omeprazole and the inferior patch reaction is a 2+ positive reaction at 96 hours to pantoprazole.

However, there are times where this approach is not sufficient. Skin prick testing (SPT) is often the next step in workup of a potential medication allergy. Interpretation of these results is often more challenging than testing to standard environmental allergens. If there is a negative reaction to SPT, the next step is intradermal testing (IDT), which has a greater sensitivity.

Both SPT and IDT should be preformed 6 weeks to 6 months after complete healing of the cutaneous lesions and at least 1 month after discontinuation of systemic immunosuppressive therapy. There are not commercially available standard preparations for most pharmaceuticals, and PPIs and H₂RAs are no exception. Parenteral preparations are preferred, but if not available, as with lansoprazole and rabeprazole, the pill form can be used. For pill form, it is best to remove the coating and grind to a fine powder.^{102,103} Parenteral preparations should be diluted in 0.9% NaCl, whereas pills can be dissolved in 0.9% NaCl or petrolatum.¹⁰⁴ For concentration, there is no reliable international consensus given the lack of multicenter studies, and therefore very limited data on the optimal concentration for H₂RA and PPIs. The “nonirritant” concentration for a given drug is typically used. For PPIs, a 10% test dose appears to be below the irritant threshold. There is even less data on H₂RA, but a 1% test dose appears nonirritant.¹⁰³

Regarding PPIs, multiple studies have investigated the usefulness of SPT and IDT as an accurate diagnostic marker of allergy. The specificity and positive predictive value have been reported to be as high as 100%, whereas the negative predictive value has ranged from 70% to 91% with a sensitivity of 58.8% to 61.3%.^{105,106} Higher rates of positive skin testing have been found in those with more severe reactions, such as bronchospasm, shock, and laryngeal edema. The above studies are in agreement that positive skin test reactions can be considered clinically relevant, and OPT does not need to be completed for a confirmatory result.¹⁰⁶ However, if there is a negative reaction to both SPT and IDT, OPT can be considered. Bonadonna et al¹⁰⁶ found that of the 41 patients with a negative skin test 3 had a positive reaction to OPT. Sánchez-Morillas et al⁵¹ reported a positive reaction to OPT in 2 of 3 patients with negative omeprazole skin tests. Kepil Özdemir et al¹⁰⁵ found that 8 of 12 patients reacted positively to

TABLE 4. Adverse Cutaneous Reactions to PPIs

Author	Clinical Manifestation	PPI
Odeh et al ⁸²	Small vessel vasculitis	Omeprazole
Sandholdt et al ⁸³	Subacute cutaneous lupus, 3 confirmed cases, 16 probable cases	Lansoprazole, omeprazole, esomeprazole, pantoprazole
Bracke et al ⁸⁴	Subacute cutaneous lupus, 2 cases	Lansoprazole
Dam et al ⁸⁵	Subacute cutaneous lupus, 2 cases	Pantoprazole, lansoprazole
Panting et al ⁸⁶	Subacute cutaneous lupus, 1 case	Lansoprazole
Mankia et al ⁸⁷	Subacute cutaneous lupus, 1 case	Omeprazole
Toms-Whittle et al ⁸⁸	Subacute cutaneous lupus, 2 cases	Omeprazole
Correia et al ⁸⁹	Discoid lupus, 1 case	Pantoprazole
Meding ⁷⁸	Allergic contact dermatitis, 2 cases	Omeprazole
Vilaplana and Romaguera ⁸⁰	Allergic contact dermatitis, 1 case	Lansoprazole
Conde-Salazar et al ⁷⁹	Allergic contact dermatitis, 2 cases	Omeprazole
Neumark et al ⁸¹	Allergic contact dermatitis, 1 case	Pantoprazole
Al-Falah et al ⁷⁶	Allergic contact dermatitis, 1 case	GastroGard*
Alwan et al ⁷⁷	Allergic contact dermatitis, 1 case	GastroGard*
Kepekci et al ⁹⁰	Fixed drug eruption, 1 case	Omeprazole
Kai et al ⁹¹	Fixed drug eruption, 1 case	Omeprazole
Morais et al ⁹²	Fixed drug eruption, 1 case	Esomeprazole
Nantes Castillejo et al ⁹³	Acute generalized exanthematous pustulosis, 3 cases	Omeprazole
Dewerd et al ⁹⁴	Acute generalized exanthematous pustulosis, 1 case	Lansoprazole
Thakor et al ⁹⁵	Toxic epidermal necrolysis, 1 case	Omeprazole
Fracaroli et al ⁹⁶	Toxic epidermal necrolysis, 1 case	Lansoprazole
Caboni et al ⁹⁷	Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, 1 case	Esomeprazole
Bourneau-Martin et al ⁹⁸	Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, 1 case	Omeprazole
Cohen ⁹⁹	Sweet syndrome, 1 case	Omeprazole, esomeprazole
Shukla et al ¹⁰⁰	Photoallergic dermatitis, 4 cases	Omeprazole, rabeprazole, pantoprazole, esomeprazole
Stenier et al ¹⁰¹	Nonspecific bullous reaction	Omeprazole

Adverse clinical manifestations documented in the literature due to PPIs.

*GastroGard is a veterinary injection used in horses. It contains 37% omeprazole.

OPT after negative skin testing. If OPT is to be completed, it must be done in a safe environment where an anaphylactic reaction can be handled appropriately.

The extent of cross-reactivity between PPIs remains unclear. A few cases have shown cross-reactivity between all 5 PPIs,^{74,107} whereas other larger studies have shown cross-reactivity between pantoprazole, omeprazole, and esomeprazole but not lansoprazole and rabeprazole.^{50,106} Lansoprazole and rabeprazole have a single documented case of cross-reactivity.¹⁰⁸ Omeprazole, pantoprazole, and esomeprazole all have substitutions on their benzimidazole ring, whereas rabeprazole and lansoprazole are substituted on the pyridine ring, suggesting this structural region plays a role in cross-reactivity.¹⁰⁸ However, Galindo et al¹⁰⁹ documented a case with cross-reactivity between omeprazole and lansoprazole.

Cross-reactivity for H₂RA, like PPIs, is unclear. Cross-reactivity between ranitidine, famotidine, and cimetidine has not been documented likely due to the significant difference in chemical structure.^{6,110–113} However, they do share 2 similar groups, the terminal nonsubstituted amino group and the furan group, which could account for some possible cross-reactivity.³⁴ The only cross-

reactivity documented was with ranitidine, hydroxyzine, and dexchlorpheniramine.¹¹⁴

For type IV hypersensitivity reactions, there are 2 ways to determine T-cell activation, patch testing and lymphocyte transformation test (LTT). Patch testing can be performed in the outpatient office setting with the results read at 48 and 72 or 96 hours. The suggested vehicle is petrolatum or 0.9% NaCl. The nonirritant concentration for PPIs is 10% to 50% in petrolatum; however, a suggested concentration for H₂RAs has not been determined.¹⁰³ The utility of LTT is limited due to the lack of availability. Lymphocyte transformation test has various detection methods, but the most widely used is the proliferation test. This involves exposing T-lymphocytes to the offending drug and measuring ³H-thymidine uptake of dividing cells. Increased uptake and thus proliferation indicates T-cell sensitization. Ghatan et al⁷³ found that 31 (32%) of 96 patients with clinical symptoms of hypersensitivity from occupational exposure to omeprazole had a positive LTT and 23 of 28 patch test–positive patients also had a positive LTT. Using patch testing as a reference, sensitivity and specificity were determined to be 82%. In addition, they found that, when combining

LTT and patch testing, there was a greater ability to identify patients with an allergy.

Since many patients take medications as needed in OTC form for gastric hyperacidity, these drugs may be overlooked as a cause of adverse events. Proton pump inhibitors are one of the most widely utilized medications, and their implication in causing cutaneous reactions is becoming increasingly more common. As with other adverse drug reactions, recognizing and stopping the causative agent is the single most important step. If therapy is needed for GERD or gastric ulcers not caused by *H. pylori*, H₂RA is a safe alternative to PPIs, and vice versa. To date, there is no evidence of cross-reactivity between H₂RA and PPIs. However, if the patient has documented *H. pylori*, all current eradication protocols include the use of a PPI. In patients with a suspected PPI allergy by skin testing, both SPT and IDT may need to be considered to help guide therapeutic decisions given the lack of alternative agents and the unclear data regarding cross-reactivity among the PPIs.

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