Proton Pump Inhibitors 14

Abstract

Proton pump inhibitors (PPIs), omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole bind irreversibly to the H^+, K^+- ATPase (the "proton pump") inhibiting its activity and decreasing gastric acid production. Systemic reactions to PPIs include anaphylaxis, urticaria, angioedema, interstitial nephritis, and thrombocytopenia. Cutaneous reactions include contact dermatitis, maculopapular and lichenoid eruptions, vasculitis, exfoliative erythrodermia, AGEP, DRESS, and SJS/TEN. Autoimmune reactions, including cutaneous lupus erythematosus, have been described. Cross-reactions between PPIs may be limited to one or two drugs or all drugs may be recognized. Cross-reaction studies so far have been based on skin testing, but the interpretations lack a quantitative basis. Successful oral desensitization following anaphylaxis to a PPI has been achieved in a few hours. Skin testing and challenge testing have been the only procedures employed to diagnose immediate reactions to PPIs. A suitable test for the detection of PPI-specific IgE antibodies is not yet available, and application of the positive basophil activation test has been limited.

Proton pump inhibitors (PPIs) reduce gastric acid production in a pronounced and sustained manner. They are the most potent of the drugs that inhibit gastric acid secretion and are now widely used, essentially replacing the formerly heavily used histamine H_2-receptor antagonists.

14.1 Chemistry

All marketed PPIs, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole are benzimidazole derivatives with the timoprazole backbone structure (Table 14.1). Esomeprazole is the *S*-enantiomer of omeprazole and dexlansoprazole the *R*-enantiomer of lansoprazole. The structures of each of these PPIs consist of substituted pyridine and a benzimidazole heterocyclic center linked by a methylsulfinyl group. Some new PPIs being developed, for example, tenatoprazole (Table 14.1), have an imidazopyridine instead of the benzimidazole ring structure. The imidazopyridine drugs have a longer half-life than the existing PPIs.

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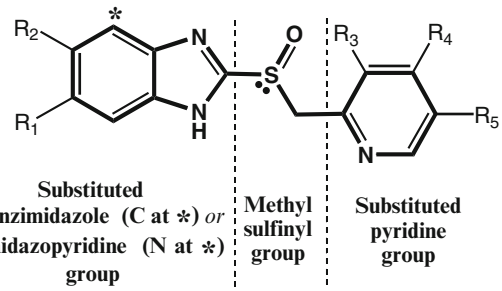
Table 14.1 Chemical structures of benzimidazole proton pump inhibitors (PPIs) showing the timoprazole backbone structure and structure of tenatoprazole, a new generation imidazopyridine PPI



General structure of PPI

Proton pump inhibitor (PPI)	Atom at pos. *	Enantiomorph at *S* sulfinyl	$-R_1$	$-R_2$	$-R_3$	$-R_4$	$-R_5$
Backbone structure							
Timoprazole	C	–	–H	–H	–H	–H	–H
Benzimidazole group							
Omeprazole[a]	C	*RS*[a]	$-OCH_3$	–H	$-CH_3$	$-OCH_3$	$-CH_3$
Esomeprazole[b]	C	*S*[b]	$-OCH_3$	–H	$-CH_3$	$-OCH_3$	$-CH_3$
Lansoprazole[c]	C	*RS*[c]	–H	–H	$-CH_3$	$-OCH_2CF_3$	–H
Dexlansoprazole[d]	C	*R*[d]	–H	–H	$-CH_3$	$-OCH_2CF_3$	–H
Rabeprazole	C	*RS*	–H	–H	$-CH_3$	$-O(CH_2)_3OCH_3$	–H
Pantoprazole	C	*RS*	$-OCHF_2$	–H	$-OCH_3$	$-OCH_3$	–H
Imidazopyridine group							
Tenatoprazole	N	*RS*	–H	$-OCH_3$	$-CH_3$	$-OCH_3$	$-CH_3$

[a]Omeprazole is a 1:1 racemic mixture of the *R*- and *S*-enantiomers
[b]Esomeprazole is the *S*-enantiomer of omeprazole
[c]Lansoprazole is a 1:1 racemic mixture of the *R*- and *S*-enantiomers
[d]Dexlansoprazole is the *R*-enantiomer of lansoprazole

14.2 Mechanism of Action

The PPIs are prodrugs, activated by exposure to pHs less than 5. Once activated, the drugs bind irreversibly to the H^+, K^+- ATPase (the "proton pump") in the parietal cell apical membrane, inhibiting its activity and decreasing gastric acid production by more than 95 %. The process is irreversible in that new enzyme needs to be produced to overcome the inhibition. PPIs have little effect on gastric acid volume and do not affect gastric motility.

14.3 Hypersensitivity Reactions to Proton Pump Inhibitors

Hypersensitivity reactions to PPIs may be mild but the spectrum of possible reactions is wide and some may be severe and life-threatening. Systemic reactions include anaphylaxis, urticaria, angioedema, acute interstitial nephritis, cytopenia, thrombocytopenia, and vasculitis. Cutaneous reactions include occupational contact dermatitis, photoallergic dermatitis, lichenoid eruption, erythema nodosum, pytiriasis rosea, exfoliative erythrodermia, acute generalized exanthematous pustulosis (AGEP), fixed drug eruption, maculopapular eruption, drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Autoimmune reactions, including cutaneous lupus erythematosus, have been described.

There are a number of reports of anaphylaxis to PPIs, particularly omeprazole and pantoprazole. This may reflect usage. Recent figures on the incidence of anaphylaxis to PPIs are hard to find but as of May 1999, the Uppsala Monitoring Centre database contained 42 reports of anaphy-

lactic reactions to the drugs with omeprazole, lansoprazole, and pantoprazole showing incidences (percentages of all reported adverse reactions) of 0.2, 0.2, and 0.4 %, respectively. Judging by the number of reports in the literature, it seems certain that the number of cases of anaphylaxis to PPIs since 1999 is considerably more than 42. Investigations of immediate reactions to PPIs have generally been carried out by skin testing, sometimes yielding results that provide information on cross-recognition between the different drugs as well as the drug(s) provoking the reaction. In one example, a patient with a severe immediate reaction to lansoprazole confirmed by skin prick testing and challenge with the drug also reacted to a 5 mg challenge with rabeprazole, despite showing negative skin reactions to that drug, omeprazole, and pantoprazole and negative challenge tests to omeprazole and pantoprazole. Possible cross-reactivity between lansoprazole and rabeprazole was also demonstrated in a separate study by intradermal tests on a patient allergic to the former drug. Investigations of immediate reactions to PPIs have revealed allergic recognition of omeprazole and lansoprazole in the same patient, and one case of hypersensitivity to omeprazole showed a prick test-positive response to lansoprazole. Other observed patterns of limited cross-reactivity include recognition of omeprazole, lansoprazole, and pantoprazole and cross-recognition between omeprazole and pantoprazole. There is also a report of a patient with anaphylaxis and a positive skin test to omeprazole and a negative skin test to pantoprazole, lansoprazole, esomeprazole, and rabeprazole. Another case report describes a patient allergic to omeprazole but tolerant to both pantoprazole and lansoprazole (esomeprazole and rabeprazole were not tested). The clinical features of immediate reactions to PPIs suggest an IgE antibody-mediated mechanism and the observed cross-reactions likely reflect antibody cross-recognition of fine structural features on the different drugs. Omeprazole and pantoprazole are structurally fairly similar; the former has a methoxy substituent on the benzimidazole group while the latter has a difluoromethoxy group at the equivalent position and an extra methoxy on the pyridine ring. Lansoprazole and rabeprazole differ only at position 4 on the pyridine ring where the former has a trifluoroethoxy and the latter a methoxypropoxy group (Table 14.1). It seems likely that structures of the two drugs are sufficiently similar to be recognized by some IgE antibodies. While these findings demonstrate limited cross-reactivities, other investigations have detected cross-reactivity covering all of the PPIs in current use. This area of PPI hypersensitivity research has essentially been based on clinical studies principally using skin testing to demonstrate cross-recognitions, and the interpretations lack a quantitative basis. Application of quantitative hapten inhibition experiments alongside skin test results are sorely needed, but this will be difficult without a suitable method for the detection of PPI-reactive IgE antibodies in allergic patients' sera.

Successful oral desensitization of a patient who experienced anaphylaxis to omeprazole was achieved after 5.6 h, starting with an initial dose of 1 μg of drug and ending with a full dose of 16 mg for a total cumulative dose of 32.6 mg. After the desensitization, the patient was able to tolerate the full dose uneventfully and the wheal size of the intradermal response to omeprazole was significantly reduced.

There appears to be fewer reports of delayed reactions to PPIs, but the range of adverse skin reactions seen is wide. Pantoprazole, for example, has been implicated in severe cutaneous responses including SJS/TEN, lichenoid eruption, exfoliative erythrodermia, and vasculitis. At least one fatal reaction has occurred following TEN induced by a PPI. Maculopapular eruptions and pruritus are frequently seen and mild in intensity. Erythrodermic reactions to omeprazole and lansoprazole and allergic contact dermatitis to lansoprazole have also been reported. A case of DRESS induced by esomeprazole is noteworthy since it involved co-sensitivity to other PPIs and suggested caution in skin testing PPIs in patients with severe reactions. Patch testing using esomeprazole as a 10 % solution gave a positive reaction at 48 and 72 h. A second series of patch tests proved positive to omeprazole and pantoprazole as well as to esomeprazole, but no

reaction was seen with rabeprazole. Histological examination of the esomeprazole-positive test showed typical signs of a delayed hypersensitivity response. At 60 h after the second tests, the patient experienced a mild erythroderma with facial edema and desquamation, indicating induction of a flare of DRESS.

14.4 Diagnosis of Hypersensitivity to Proton Pump Inhibitors

Skin testing and to a lesser extent challenge testing have almost invariably been the only clinical or laboratory test procedures employed in the diagnosis of immediate reactions to PPIs. Prick test concentrations used have shown up to a tenfold variation: for omeprazole and pantoprazole, 4–40 mg/ml; esomeprazole, 20–40 mg/ml; lansoprazole, 3–30 mg/ml; and rabeprazole, 10–20 mg/ml. Solutions of omeprazole and pantoprazole have been prepared by dissolving lyophilized drug in physiological saline while solutions of the other three PPIs are usually formulated from crushed and powdered tablets. Reported investigations have not always included results of skin tests on nonallergic controls. For intradermal testing, the concentration ranges used have been more consistent—omeprazole and pantoprazole, 0.04–8 mg/ml; lansoprazole, 0.015–3 mg/ml; esomeprazole, 0.02–2 mg/ml; rabeprazole, 0.01–2 mg/ml. These concentrations generally represent 1:10, 1:100, and 1:1,000 serial dilutions of the prick test concentrations with testing starting at the lowest concentration and stepping up until a positive reaction results. So far, there is limited information available on patch testing with PPIs. Test concentrations employed are in the range 10–30 % in petrolatum or aqueous medium, and tests are generally read at least twice after 48–96 h. If cutaneous reactions are severe, great caution should be exercised.

Oral challenge with lansoprazole of a patient who experienced an anaphylactic-type reaction to the drug provides an example of the use of this test in confirming a diagnosis of an immediate reaction to a PPI. Three doses of lansoprazole, 7.5, 15, and 30 mg, were given at 60 min intervals. Twenty minutes after the third and final dose, that is after a total dose of 52.5 mg, the patient reacted with erythema of palms, itching, rash, and malaise.

A recently published (2012) European multicenter study compared the diagnostic accuracy of skin and oral provocation tests in patients with immediate hypersensitivity to PPIs. Patients with reactions that were not immediate were excluded. Skin prick tests were performed with solutions of omeprazole, esomeprazole, pantoprazole, and rabeprazole at 40 mg/ml and lansoprazole, 30 mg/ml. Omeprazole, esomeprazole, and pantoprazole were used in intradermal tests at 0.4 and 4 mg/ml. Oral provocation tests carried out on some patients after skin testing consisted of the administration of four talc capsules on day one followed on day two by lansoprazole (5, 10, 15 mg) or one of the other four drugs (5, 5, 10, 20 mg) at 30 min intervals. Skin tests were positive in 12 of 53 patients; four of these underwent provocation testing with the suspected PPI and in each case a positive response was obtained. Provocation tests on the 41 patients with a negative skin test showed three more positive reactors. For the skin tests, specificity and the positive predictive value were both 100 %. The negative predictive value was 91.9 %. A higher frequency of skin test positivity occurred in patients with severe reactions and cross-reactions consistent with previous observations were observed. The study's authors concluded that skin testing with PPIs on patients with immediate hypersensitivity to these drugs is a useful diagnostic test, and the test has the additional advantage of allowing the clinician to avoid oral challenges.

So far a suitable test for the detection of PPI-specific IgE antibodies does not appear to be available. There are at least two reports of a positive basophil activation test on patients allergic to omeprazole—one utilizing the CD63 basophil marker that was positive to omeprazole but negative to pantoprazole and the other detected by the flow-cytometric cellular allergen simulation test (FAST).

14.5 Proton Pump Inhibitors, Gastroesophageal Reflux Disease, and Asthma

There appears to be a higher incidence of asthma in children with gastroesophageal reflux disease (prevalence estimated to be 34–89 %), and this has prompted the suggestion, and the belief seemingly supported by some studies, that PPI treatment of these children may lead to an improvement in asthma symptoms. Three randomized trials showed that PPIs had a beneficial effect on asthma symptoms but one randomized, double-blind, placebo-controlled trial failed to show that omeprazole improved symptoms. At present, there is not enough data from well constructed and controlled clinical trials to reach a confident and conclusive decision on this question.

14.6 Other Safety Concerns with Proton Pump Inhibitors

Besides hypersensitivity responses to PPIs, there are at least four other specific concerns related to the interactions and/or direct effects of PPIs in humans. The oral antiplatelet drug clopidogrel is used to inhibit blood clots. PPIs inhibit the bioactivation of clopidogrel to its active metabolite and reduce the antiplatelet effects of the drug. It has been suggested that this may lead to an increased risk of vascular events. The results of a recent randomized control trial with clopidogrel and omeprazole do not add support to this belief, but the makers of PPIs have agreed to work with the FDA to conduct studies to obtain additional information that will allow a better understanding of the effects of PPIs on clopidogrel. A second concern associated with PPIs is a suggested link between the drugs and fractures. Some believe that this could be related to altered absorption of calcium, vitamin B_{12}, or iron. Clear evidence to support an association with bone fractures is, at present, lacking and no convincing mechanism has been suggested, so the alleged association remains to be resolved. Thirdly, the possibility that long-term PPI use might lead to hypomagnesemia has led the FDA to suggest that serum magnesium levels of patients taking PPIs should be monitored. Again, the mechanism of such an effect of the PPIs is unclear. More clinical data are needed in the case of each of these three concerns and until that is the situation, clinicians and researchers should remain aware and keep abreast of developments in each area. Lastly, the use of PPIs has been shown to be a significant risk for both community- and hospital-acquired pneumonia.

Summary

- All marketed PPIs, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole are benzimidazole derivatives. Some new PPIs being developed have an imidazopyridine instead of the benzimidazole ring structure.
- The PPIs are prodrugs, activated by exposure to pHs less than five. Once activated, the drugs bind irreversibly to the H^+, K^+- ATPase (the "proton pump") in the parietal cell apical membrane, inhibiting its activity and decreasing gastric acid production by more than 95 %.
- Systemic reactions to PPIs include anaphylaxis, urticaria, angioedema, interstitial nephritis, cytopenia, thrombocytopenia, and vasculitis.
- Cutaneous reactions include occupational contact dermatitis, photoallergic dermatitis, pruritus, maculopapular eruptions, vasculitis, lichenoid eruption, erythema nodosum, pityriasis rosea, exfoliative erythrodermia, AGEP, fixed drug eruption, DRESS, and SJS/TEN. Autoimmune reactions, including cutaneous lupus erythematosus, have been described.
- Patterns of limited cross-reactivity include recognition of omeprazole, lansoprazole, and pantoprazole and cross-recognition between omeprazole and pantoprazole. Other investigations have detected cross-reactivity covering all of the PPIs in current use.
- Cross-reaction studies so far have been based on skin testing, and the interpretations lack a

quantitative basis. Development of IgE tests and application of quantitative hapten inhibition experiments alongside skin test results are needed.

- Successful oral desensitization of a patient who experienced anaphylaxis to omeprazole was achieved after 5.6 h.
- Skin testing and to a lesser extent challenge testing have almost invariably been the only clinical or laboratory test procedures employed in the diagnosis of immediate reactions to PPIs.
- A recently published multicenter study compared the diagnostic accuracy of skin and oral provocation tests in patients with immediate hypersensitivity to PPIs. For the skin tests, specificity and the positive predictive value were both 100 %. The negative predictive value was 91.9 %.
- A suitable test for the detection of PPI-specific IgE antibodies is not yet available, and application of the positive basophil activation test has been limited.
- Other safety concerns with PPIs include the suggested inhibition of the antiplatelet effects of clopidogrel leading to an increased risk of vascular events, and associations with bone fractures, hypomagnesemia, and pneumonia.

Further Reading

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