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Long lasting inhibitors of the gastric H,K-ATPase

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Abstract/Summary

Proton pump inhibitors (PPIs) are acid-activated prodrugs which covalently bind to the gastric H,K-ATPase on its luminal surface. Only active pumps can be inhibited. The short plasma residence time of current PPIs prevents inhibition of pumps synthesized or activated after the PPI has disappeared, limiting the degree of acid inhibition even with BID administration. PPIs with a longer residence time should improve acid control. Various K^+ competitive inhibitors of the pump are being developed (APAs or PCABs), with the advantage of complete inhibition of acid secretion independent of pump activity. Early data on these suggest that twice a day administration would improve acid control compared to PPIs.

Keywords

the gastric H,K-ATPase; proton pump inhibitor; acid pump antagonist; potassium-competitive acid blocker; prodrug

Introduction

Acid related diseases, such as peptic ulcer disease (PUD), gastro-esophageal erosive reflux disease (GERD), and non-erosive reflux disease (NERD) are an extremely common set of human ailments. Over recorded history there always have been remedies for these, such as calcium bicarbonate and other antacids and atropine (Bella Donna or deadly nightshade). Poor efficacy or side effects limited the use of these agents and until the last quarter of the twentieth century, surgery was the only effective treatment.

The introduction of histamine-2 receptor antagonists (H2RAs) revolutionized the treatment or peptic ulcer disease by being the first medications to provide benefit with few side effects [1]. Then the introduction of proton pump inhibitors (PPIs) revolutionized the treatment of gastroesophageal reflux disease that was somewhat refractory to H2RAs [2]. In fact, the presence of PPIs as a therapeutic modality led to an explosion of publications on GERD and recognition of the expansion of this disease, in contrast to the decline of peptic ulcer disease in the Western world, probably due to declining infection with *Helicobacter pylori*.

The PPIs in clinical use are substituted pyridylmethylsulfinyl benzimidazoles that have a unique mechanism of action in current pharmacotherapy (figure 1). First there is selective accumulation of the inactive compound in the acidic space of the acid-secreting parietal cell and this is then followed by acid activation to the species that can react with the gastric H,K-ATPase, and the proton pump of the parietal cell. Hence they are prodrugs.

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They are all membrane permeant weak bases with one pK_a (pK_a1) at about 4.0 with the exception of rabeprazole that has this pK_a at ~5.0. This pK_a has two quite distinct consequences. Firstly, it determines the ability of these drugs to accumulate selectively in the highly acidic space of the parietal cell as compared to any other acidic space such as lysosomes or distal renal tubular contents. There is no other membrane-enclosed space with a pH low enough to accumulate the PPIs. Secondly, it contributes to the acid stability of the PPIs. If the pK_a is too high, the drug is relatively unstable at neutral pH.

Following accumulation of the drug due to the protonated pyridine, there is a second protonation on the imidazole N of the benzimidazole (pK_a2), resulting in a nucleophilic attack of the pyridine N on the 2C of the benzimidazole to form a planar tetracyclic derivative that then forms a sulfenic acid that reacts with luminally exposed cysteines of the H,K-ATPase (figure 1). The PPIs are thus acid-activated prodrugs. This gives them a large window of safety or therapeutic index, due to both accumulation at their target and the need for high acidity for activation. All of the PPIs form disulfides with at least two of the cysteines in this region, cysteine 321, 813, 822 and 892. The first 3 are in the transport domain of the pump and therefore inhibit the pump by covalent bond formation. The rate of conversion to reactive species varies between the current PPIs, and is a reflection of the degree of protonation of both the pyridine and the benzimidazole. The rate of activation is rabeprazole>omeprazole=lansoprazole>pantoprazole and this reflects the pK_a1 of rabeprazole and the pK_a2 of the other PPIs, with the pK_a2 of pantoprazole being significantly lower than those of omeprazole and lansoprazole.

From this, at first glance, it would appear that PPIs would completely inhibit acid secretion, a desirable outcome for treatment of acid related diseases. However, several factors prevent this from occurring. Firstly the pump has to be making acid for the compounds to convert to active moieties. Secondly, new pumps are continually being synthesized (about 25% per day in the rat) therefore the PPI needs to be in the blood for a protracted period of time, certainly longer than the 90 min half-life of the current PPIs. If there is circadian rhythm of synthesis, such that more pumps are renewed at night than during the day, night time efficacy of acid inhibition will be even more significantly impaired. Thirdly, with some of the PPIs there is partial reversal of the disulfide bonds [3], although the significance of this property is uncertain.

The need for acid production by the pump defines not only the optimal dosing regimen but also their effect as a function of day of dosing. The first goal of therapy is to provide the drug at the time when as many pumps are active as possible. This is achieved by providing the drug about 1hr before breakfast for once a day dosing and, if needed, a second dose before dinner. Since only a fraction of the proton pumps are active at any time, but those are covalently inhibited, there is a dependence of effect on the number of days of dosing. Typically the percentage of time with intragastric pH >4.0 was about 67% with once a day and 81% with twice a day dosing of esomeprazole [4]. The lowest pH with such treatment is found at night and it is very hard to achieve a neutral pH at this time with any current oral PPI even with bid dosing since drug will be absent from the blood during pump synthesis and activation after about midnight. The gastric H,K-ATPase secretes ~160 mM HCl and relatively few pumps have to be active to drop the pH to < 3.0 in the absence of buffering by food. To avoid low pH at night, the time of exposure of the pump to the PPI drug has to be increased.

Peculiarly, although most patients respond adequately to once a day dosing, a significant fraction (~25%) do not and then bid dosing is used, however with rather little improvement. These patients for the purposes of this review are classified as “poor-responders”. The ideal drug would provide a pH ~ 5.0 for 24hr with once a day dosing.

Given covalent inhibition, there is not a simple relationship between pharmacokinetics and effect, as is the case for reversible inhibitors. Hence, the area under the curve (AUC) has been used as a predictor of the effect of PPIs. The drawback of this parameter is that the initial peak is largely wasted drug, making this surrogate parameter not entirely reliable. Also the effect of a given level of drug depends also on its rate of conversion to the active principle. Thus with slow conversion even a high level of a PPI with a high AUC will not predict the efficacy of the drug as is the case for pantoprazole. An alternative predictor of efficacy would be the time above threshold in the blood, at about 50 ng/ml of PPI although this threshold value is dependent on the rate of activation of the prodrug.

An apparent innovation was introduced by the S-enantiomer of omeprazole, esomeprazole, which has a slightly delayed metabolism compared to the R-enantiomer. In comparative studies, 40mg esomeprazole was compared to 20 mg of the racemic omeprazole and some improvement in outcome was observed. However, the active compound generated in acid from esomeprazole has no chiral center and is identical to that formed from omeprazole. Recently, the R-enantiomer of lansoprazole has been introduced with a delayed release formulation.

There are several conceptual means of improving acid inhibition with the H,K- ATPase as the target. Firstly, a new core structure can be generated with slower metabolism to improve the residence time in the blood hence exposure to active pumps. A delayed release formulation can be established also with the aim of increasing exposure. A prodrug of a PPI, actually a prodrug of a prodrug, can be synthesized so as to delay absorption and thus also to increase exposure. Or, a novel mechanism can be used where pump inhibition is reversible. These will each be discussed in turn.

(a) Tenatoprazole

As can be seen from the structure shown in figure 2, this compound is an imidazo-pyridine, not a benzimidazole. This structure has a much slower metabolism that the benzimidazole class giving a plasma half life of about 6 hr. The structure results in a fairly normal pK_a 1 but a marked reduction in the pK_a2 such that the rate of activation of this compound to the sulfenic acid required to react with the H,K-ATPase is considerably slower than, for example, omeprazole or lansoprazole (figure 2). Ilaprazole is a compound also in development with a longer half life.

The patent on the core structure of tenatoprazole was extended by synthesis of the S-enantiomer, with superior pharmacokinetics. It is still under development. Early human studies have shown that administration of 40 mg at night provides superior acid control as compared to esomeprazole, and also better day time control. However, an intragastric pH <2.0 is found even with tenatoprazole early after dosing [5,6]. This is due to the slow onset of action. It is not known whether twice a day (BID) dosing of this drug would dramatically improve pH control.

Of particular significance is the periods as shown in figure 3 where intragastric pH falls to ~2.0 in the case of esomeprazole and to ~3.0 in the case of tenatoprazole. At such a pH, it may be expected that symptoms and damage to the esophagus can continue, accounting for the poor response to PPIs in 25% of patients. In initial analysis of the response of patients to H2 receptor antagonists or omeprazole, the concept of maintaining pH > 4.0 for 16–18 hr per day predicted excellent GERD healing and symptom relief [7]. However, the periods where the pH falls to < 3.0 must be taken into consideration for the 25% of PPI-poor responders.

This excursion to highly acidic pH can also account for the ~25% failure of eradication of *Helicobacter pylori* using bid triple therapy consisting of a PPI and amoxicillin and clarithromycin. These antibiotics require cell division for their activity and at a pH <3.0 the organisms revert to stationary phase and hence lose antibiotic sensitivity. In particular, clarithromycin resistance accounts for an increasing number of patients who fail to eradicate on triple therapy today [8]. A more prolonged acid suppression is necessary for effective eradication and this is achieved in “slow omeprazole metabolizers” where a mutation in CYP219 prolongs the residence time of omeprazole in the blood, and greatly improves the efficacy of triple therapy even allowing dual therapy with amoxicillin as the only antibiotic (figure 4) [9]. Relatively few individuals have mutations in CYP219 but the data illustrate the advantage of better acid control for eradication.

The data in figure 4 not only emphasize the progressive failure of triple therapy eradication in the majority of infected subjects but also speak to the general experience that bid therapy does not change poor responders to responders.

(b) Kapidex

Recently a novel formulation of the R-enantiomer of lansoprazole has been introduced. This is a dual release formulation of 60mg of the PPI with normal enteric coating releasing at around pH 5.0 and a coating releasing dexlansoprazole some hours later.

There was no statistically significant difference in healing between the 60mg dose and regular 30mg lansoprazole. However, there was an improvement in the time above pH 4.0, 71% relative to 60% but mean pH was 4.55 relative to lansoprazole at 4.13 [10]. This improvement is similar to what has been claimed for esomeprazole.

The biphasic PK profile for this formulation is shown in figure 5 for first day treatment that is the same as day 5, showing clear superiority 4 to 8hr after dose but not during the night. This profile might explain the small increase in 24hr pH since this would reflect mainly the low pH at night [11,12].

(c) Alevium

Another method not requiring alternative formulation is to make a derivative of a PPI that is absorbed throughout the small intestine and not just the duodenum like all the PPIs. Of various derivatives tested, a sulfonamide derivative, the phenoxyacetic acid sodium salt derivative of omeprazole seems to be a candidate drug with several desirable properties. Its structure is shown in figure 6.

Its properties can be predicted from its structure and pharmacokinetics.

1. Since one of the benzimidazole nitrogens is substituted, the compound is acid stable unlike any other PPI hence not requiring enteric coating. Further it is neutral pH stable, hence not requiring alkaline solutions for stability in IV formulation, distribution or administration.
2. It is slowly absorbed throughout the small intestine but then rapidly hydrolyzed in the blood to omeprazole and the sulfonic acid. Only trace quantities of the intact molecule are found in humans hence its safety profile should resemble that of omeprazole
3. It is not genotoxic and no adverse events were found in either rats or dogs after dosing for 3 months at 1gm/kg in rat and 500mg/kg in dogs
4. The effect of various doses in man showed a linear dose relationship with no evidence for saturation hence movement across the gut is by simple diffusion

5. The PK profile in human volunteers is shown in figure 7 following administration of 600mg alevium [13]. This shows the longer residence time above 50ng/ml from Alevium compared to esomeprazole.

It can be seen that there is great prolongation of the blood level of omeprazole and as found for omeprazole there is increased bioavailability after 5 days dosing. But significantly, there is prolongation of the residence time of omeprazole in the blood so that there is drug present at sufficient levels over 24 hours after 5 days administration. This leads to considerable improvement in the profile of intragastric pH as shown in figure 8.

As seen for esomeprazole, there is a period of high acidity in the morning and for about 6 hrs during the night, acidity clearly sufficient to potentially cause damage and symptoms and prevent *H. pylori* from entering growth phase. With once a day Alevium, the pH is stably maintained at > 4.0. Averaging pH values over 24 hours or at night shows the remarkable advantage of Alevium not only at night but also during the day [13].

(d) Acid pump antagonists (or Potassium Competitive Acid Blockers)

Besides PPIs, another type of the proton pump inhibitor was developed. This class of the inhibitor blocks acid pumping by inhibiting K^+ competitively, so this class is called either acid pump antagonists (APAs) or potassium-competitive acid blockers (PCAB). The first core structure of an APA developed in 1980s was an imidazo-pyridine. A typical structure of this class is SCH28080. Following SCH28080, many different core structures were made. Some of these APAs are shown in figure 9.

The inhibition by APAs is expected to be fast and effective since APAs do not require acid-activation. Further the pump is inhibited without any proton secretion occurring. Data in human show the expected rapid and virtually complete inhibition by APAs (PCABs), For example, in healthy volunteers, high doses of AZD0865 resulted in over 95%inhibition of acid secretion within 1 hr after oral dosing [14]. Unlike the PPIs, APAs' duration of inhibition is determined entirely by their level in the blood because APA is a reversible K-competitive antagonist. Also, there will not be the prolongation of inhibition as found in the case of the PPIs where the half-life of the covalent bond is much longer than the half-life of the PPI in the blood. Their chemical stability will allow use of standard timed release formulations to prolong their plasma half life and improve efficacy.

This inhibitor exhibit a classical (sigmoid) dose–response profile, with the magnitude and duration of effect being determined by dose, pK_a, and plasma half-life. AZD0865 demonstrated a dose–effect relationship with a dose-dependent duration of inhibition of acid secretion; more than 95% inhibition was sustained for up to 15 hr for 0.8 and 1 mg/kg doses [14]. Even though AZD0865 provided a faster onset of acid inhibition with a dose-dependent duration of activity, a clinical study showed no clinical benefit over esomeprazole [15,16]. With respect to healing of reflux esophagitis, healing rates of AZD0865 were similar to esomeprazole at four weeks treatment, about 81–82% [16]. This study was done using 1,521 patients with Los Angeles A–D esophagitis and heartburn of moderate or severe. In a study of a randomized, comparative trial of AZD0865 and esomeprazole for the treatment of patients with nonerosive reflux disease (NERD) using a total of 1,469 patients, AZD0865 did not provide clinical benefit over esomeprazole 20 mg in the management of patients with NERD [15]. However, the data suggest that BID dosing would improve outcome of AZD0865 as compared to esomeprazole. The evidence suggesting some hepatotoxicity hindered further exploration of this drug.

Revaprazan (YH1885) was the first APA clinically used in East Asia. Revaprazan is a pyrimidine derivative, N-(4-fluorophenyl)-4,5-dimethyl-6-(1-methyl-1,2,3,4-

tetrahydroisoquinolin-2-yl)pyrimidin-2-amine hydrochloride. In human study, revaprazan reached peak levels at 1.3 to 2.5 hours after single-dose administration and then declined monoexponentially with a terminal half-life of 2.2 to 2.4 hours. Revaprazan showed linear pharmacokinetic characteristics, and little accumulation occurred after multiple administrations. Mean pH at Day 1 and Day 7 was 4.6 and 4.9 respectively at 300 mg once-daily oral dose. Time at pH >4 was 61.7% at day 1 and 65.6% at day 7 [17]. The result was very similar to those of multiple-dose study of esomeprazole except that day 1 data did not change on day 5.

A fused ring system of an imidazopyridine is soraprazan, which was developed by Altana. Soraprazan inhibited H,K-ATPase with IC_{50} of 0.1 μM, K_i of 6.4 nM, with a K_d of 26.4 nM [18]. However, there is, as yet, is no detailed clinical data of this compound. Another different core structure is CS-526. CS-526 has the pyrrolopyridazine structure. CS-526 inhibited H,K-ATPase activity in a concentration-dependent manner, with an IC_50 value of 61 nM. The inhibitory effect of CS-526 on H,K-ATPase activity was very potent [19]. There are no clinical data available. Although reported clinical studies of once a day APAs showed no benefit over esomeprazole, however, BID dosing of APA is expected to show superiority over single dose of esomeprazole. A new type of APA was developed by Takeda pharmaceutical company [20]. One of the typical structures is shown in figure 9 as ‘Takeda compound’. Some of the pyrrole compound showed an IC_{50} value of 9–30 nM. One of this class of compound is under clinical trials.

Expert commentary

There appears to be a broad perception that acid related diseases are a satisfied market. Unfortunately, this is not a correct view. Clearly about 25% of patients continue with GERD symptoms, especially at night and with resistance to clarithromycin also approaching 25% preventing *H. pylori* eradication, novel methods of acid control are required. This also ignores difficult therapy of Zollinger-Elison syndrome and poor response of Barrett’s esophagus.

Five-year view

It seems highly likely that newer methods of acid control will make their appearance, In particular long acting acid pump antagonists (APA) will be introduced perhaps for either OD or BID therapy and longer residence time PPIs will also find the market. With superior acid control, these new drugs will likely become the medications of choice, as happened with PPIs as compared to H2RAs.

Key issues

- Mechanism of action of PPIs
- Acid Conversion of PPIs to active drug
- Different PPIs advantages
- Importance of residence time of PPIs for better acid control
- OD compared to BID dosing
- Structures of improved PPIs
- Novel formulation of PPIs for improved plasma residence time
- The possible role of APAs or PCABs in future therapy
- APA or PCAB structures

- Decreasing success of triple therapy for eradication of *H. pylori*

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References

1. Black JW, Duncan WAM, Durant CJ, Ganellin CR, Parsons ME. Definition and antagonism of histamine H2 receptors. Nature 1972;236:385–90. [PubMed: 4401751]
2. Sachs G, Shin JM, Vagin O, Lambrecht N, Yakubov I, Munson K. The gastric H,K ATPase as a drug target: past, present, and future. J Clin Gastroenterol 2007;41(6 Suppl 2):S226–42. [PubMed: 17575528]
3. Shin JM, Sachs G. Restoration of acid secretion following treatment with proton pump inhibitors. Gastroenterology 2002;123(5):1588–97. [PubMed: 12404233]
4. Spechler SJ, Barker PN, Silberg DG. Intragastric acid control in patients who have Barrett's esophagus: comparison of once- and twice-daily regimens of esomeprazole and lansoprazole. Aliment Pharmacol Ther. 2009 e-published.
5. Galmiche JP, Bruley Des Varannes S, Ducrotte P, Sacher-Huvelin S, Vavasseur F, Taccoen A, et al. Tenatoprazole, a novel proton pump inhibitor with a prolonged plasma half-life: effects on intragastric pH and comparison with esomeprazole in healthy volunteers. Aliment Pharmacol Ther 2004;19(6):655–62. [PubMed: 15023167]
6. Galmiche JP, Sacher-Huvelin S, Bruley des Varannes S, Vavasseur F, Taccoen A, Fiorentini P, et al. A comparative study of the early effects of tenatoprazole 40 mg and esomeprazole 40 mg on intragastric pH in healthy volunteers. Aliment Pharmacol Ther 2005;21(5):575–82. [PubMed: 15740541]
7. Bell NJ, Hunt RH. Role of gastric acid suppression in the treatment of gastro-oesophageal reflux disease. Gut 1992;33(1):118–24. [PubMed: 1346769]
8. Romano M, Iovene MR, Russo MI, Rocco A, Salerno R, Cozzolino D, et al. Failure of first-line eradication treatment significantly increases prevalence of antimicrobial-resistant Helicobacter pylori clinical isolates. J Clin Pathol 2008;61(10):1112–5. [PubMed: 18755715]
9. Padol S, Yuan Y, Thabane M, Padol IT, Hunt RH. The effect of CYP2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: a meta-analysis. Am J Gastroenterol 2006;101(7):1467–75. [PubMed: 16863547]
10. Katz PO, Koch FK, Ballard ED, Bagin RG, Gautille TC, Checani GC, et al. Comparison of the effects of immediate-release omeprazole oral suspension, delayed-release lansoprazole capsules and delayed-release esomeprazole capsules on nocturnal gastric acidity after bedtime dosing in patients with night-time GERD symptoms. Aliment Pharmacol Ther 2007;25(2):197–205. [PubMed: 17229243]
11. Metz DC, Howden CW, Perez MC, Larsen L, O'Neil J, Atkinson SN. Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis. Aliment Pharmacol Ther 2009;29(7):742–54. [PubMed: 19210298]
12. Metz DC, Vakily M, Dixit T, Mulford D. Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy. Aliment Pharmacol Ther 2009;29(9):928–37. [PubMed: 19298580]
13. Hunt RH, Armstrong D, Yaghoobi M, James C, Chen Y, Leonard J, et al. Predictable prolonged suppression of gastric acidity with a novel proton pump inhibitor, AGN 201904-Z. Aliment Pharmacol Ther 2008;28(2):187–99. [PubMed: 18445141]
14. Nilsson C, Albrektson E, Rydholm H, Rohss K, Hassan-Ali M, Hasselgren G. Tolerability, pharmacokinetics and effects on gastric acid secretion after single oral doses of the potassium-competitive acid blocker AZD0865 in healthy male subjects. Gastroenterology 2005;128 (4 Suppl 2):A528.

15. Dent J, Kahrilas PJ, Hatlebakk J, Vakil N, Denison H, Franzen S, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. Am J Gastroenterol 2008;103(1):20–6. [PubMed: 18184117]

16. Kahrilas PJ, Dent J, Lauritsen K, Malfertheiner P, Denison H, Franzen S, et al. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. Clin Gastroenterol Hepatol 2007;5(12):1385–91. [PubMed: 17950677]

17. Yu KS, Bae KS, Shon JH, Cho JY, Yi SY, Chung JY, et al. Pharmacokinetic and pharmacodynamic evaluation of a novel proton pump inhibitor, YH1885, in healthy volunteers. J Clin Pharmacol 2004;44(1):73–82. [PubMed: 14681344]

18. Simon WA, Herrmann M, Klein T, Shin JM, Huber R, Senn-Bilfinger J, et al. Soraprazan: setting new standards in inhibition of gastric acid secretion. J Pharmacol Exp Ther 2007;321(3):866–74. [PubMed: 17369284]

19. Ito K, Kinoshita K, Tomizawa A, Inaba F, Morikawa-Inomata Y, Makino M, et al. Pharmacological profile of novel acid pump antagonist 7-(4-fluorobenzyloxy)-2,3-dimethyl-1-{[(1S,2S)-2-methyl cyclopropyl]methyl}-1H-pyrrolo[2,3-d]pyridazine (CS-526). J Pharmacol Exp Ther 2007;323(1):308–17. [PubMed: 17630360]

20. Kajino, M.; Nishida, H.; Arikawa, Y.; Hirase, K.; Ono, K. inventor Takeda Pharmaceutical Company, assignee. Pyrrole compounds. WO 2008/108380 A2. 2008.

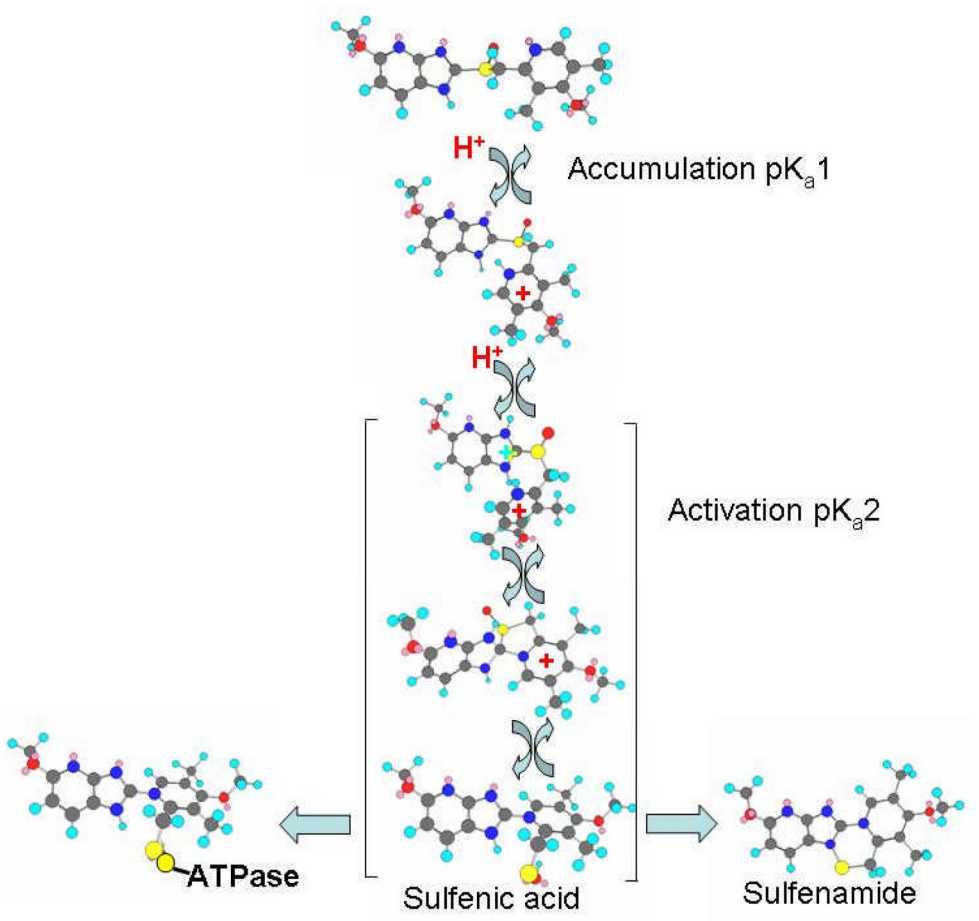

Figure 1.

PPIs are pyridinylmethylsulfinyl benzimidazole compounds which are weak bases. These have two pK_as. One is the pyridine pK_a and the other is the benzimidazole pK_a. The pyridine pK_a1 enables selective PPI accumulation in the acidic canaliculus of the parietal cell. Protonation of benzimidazole ring enhances electron deficiency at C-2 position allowing intramolecular rearrangement to the active form. The active form is the sulfenic acid and/or cyclic sulfenamide, and reacts with luminal cysteine thiols of the enzyme to inhibit the enzyme activity.

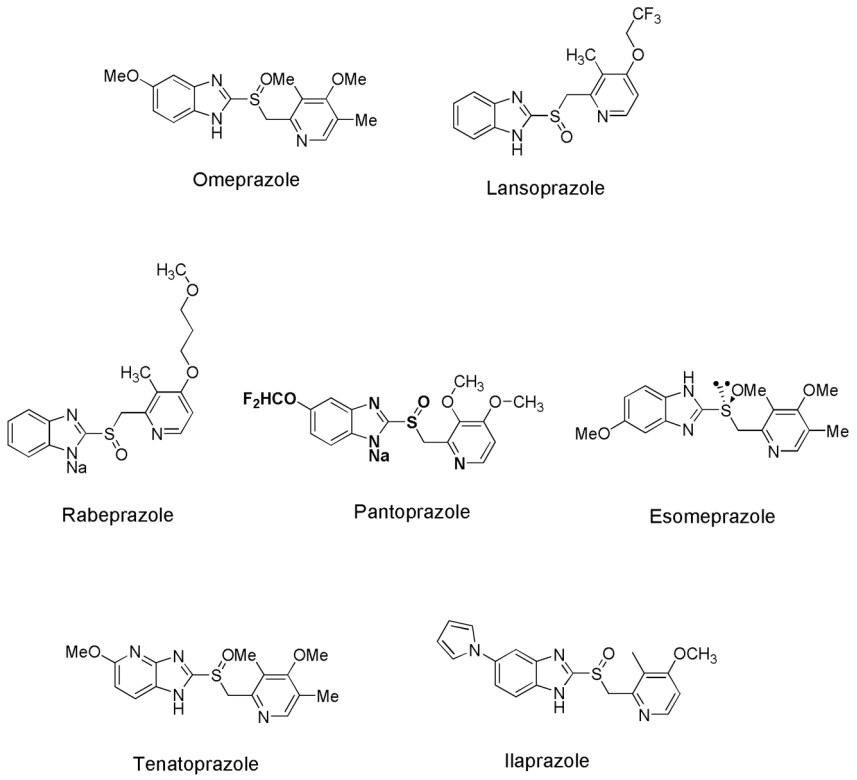

Figure 2.
Structures of the proton pump inhibitors

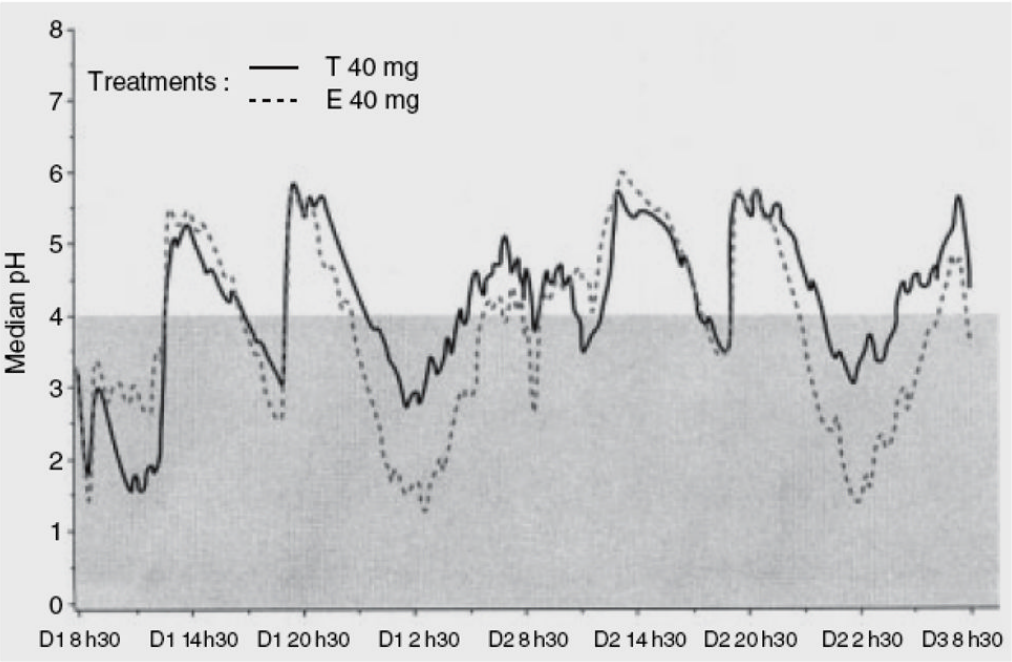

Figure 3.

Profile of the median pH curves over 48 hours comparing esomeprazole with tenatoprazole. D1 and D2 represent first day and second day respectively. T40 mg and E40 mg represent tenatoprazole 40 mg and esomeprazole 40 mg respectively. This figure is cited from the work of Galmiche et al [6]. There is improvement in pH control with tenatoprazole but still several excursions to pH < 4.0

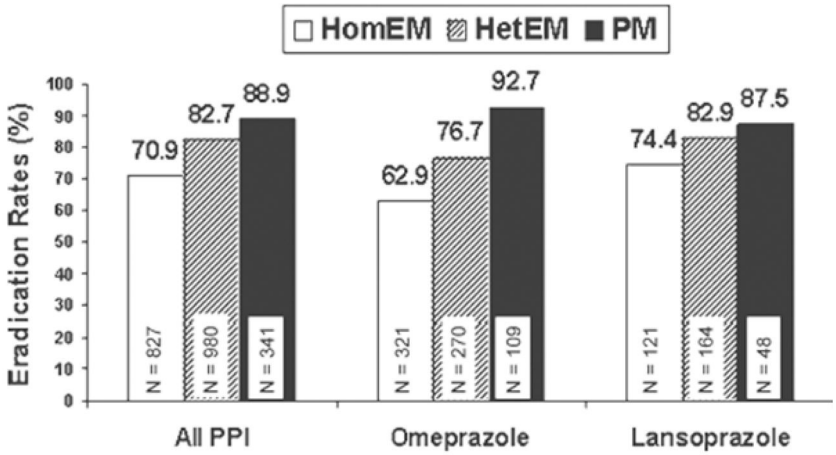

Figure 4.
Pooled *H. pylori* eradication rates calculated for all PPIs combined and for omeprazole, lansoprazole, and rabeprazole (N=number of patients). This is cited from the work of Padol et al [9].

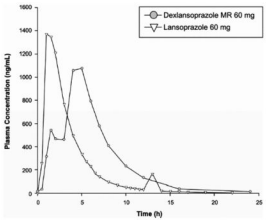

Figure 5.
Mean plasma concentration-time profiles from two separate trials evaluating dexlansoprazole MR 60 mg or lansoprazole 60 mg on day 5 in healthy subjects. This is cited from the work of Metz et al [11,12].

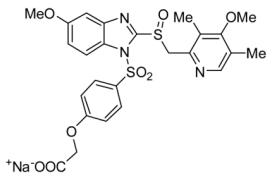

Figure 6.
Chemical structure of Alevium (AGN201904Z)

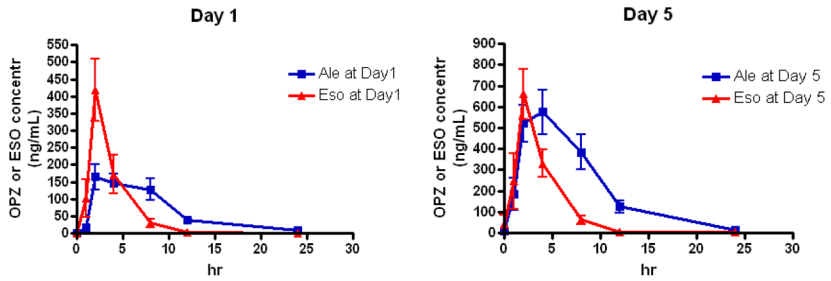

Figure 7.
Mean plasma concentration-time profiles from two separate trials evaluating at Day 1 and Day 5. This is cited from the work of Hunt et al [13].

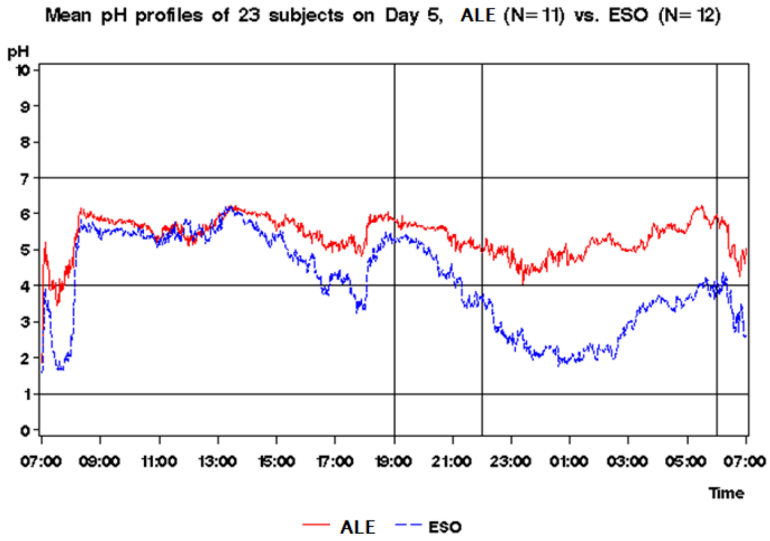

Figure 8.
Comparison of median 24-h pH profile for Alevium (AGN 201904-Z) and esomeprazole

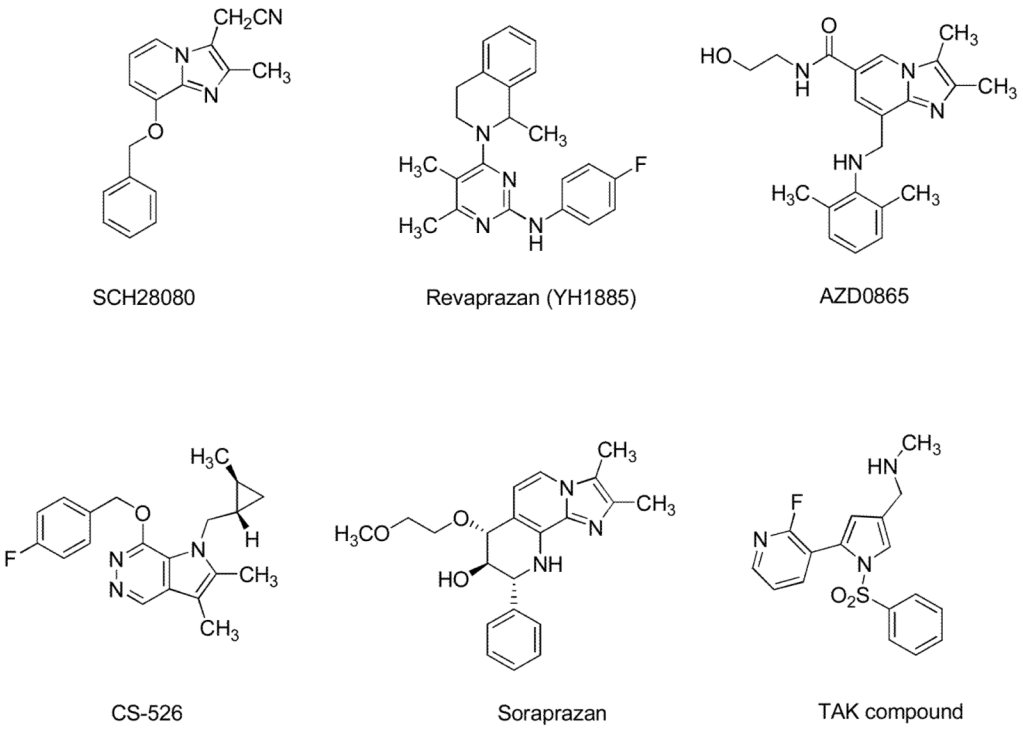

Figure 9.
Acid pump antagonists. Revaprazan is being used in clinics in east Asia. The others are under development except for SCH 28080.