

## Review article: the clinical pharmacology of proton pump inhibitors

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### SUMMARY

Proton pump inhibitors inhibit the gastric H<sup>+</sup>/K<sup>+</sup>-ATPase via covalent binding to cysteine residues of the proton pump. All proton pump inhibitors must undergo acid accumulation in the parietal cell through protonation, followed by activation mediated by a second protonation at the active secretory canaliculus of the parietal cell.

The relative ease with which these steps occur with different proton pump inhibitors underlies differences in their rates of activation, which in turn influence the location of covalent binding and the stability of inhibition. Slow activation is associated with binding to a cysteine residue involved in proton transport that is located deep in the membrane. However, this is inaccessible to the endogenous reducing agents responsible for restoring H<sup>+</sup>/K<sup>+</sup>-ATPase activity, favouring a longer duration of gastric acid inhibition. Pantoprazole and tenatoprazole, a novel proton pump inhibitor which has an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors, are activated more slowly than other proton pump inhibitors but their inhibition is resistant to reversal. In addition, tenatoprazole has a greatly extended plasma half-life in comparison with all other proton pump inhibitors.

The chemical and pharmacological characteristics of tenatoprazole give it theoretical advantages over benzimidazole-based proton pump inhibitors that should translate into improved acid control, particularly during the night.

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## TARGETS FOR INHIBITING ACID SECRETION BY THE PARIETAL CELL

The gastric acid pump is an ATPase present in cytoplasmic membranes of the resting parietal cell. On activation, the pump is translocated to the canalicular membrane, where it pumps out  $H^+$  ions into the canalicular space in exchange for  $K^+$  ions. Gastric acid secretion by the parietal cell is controlled through food-stimulated and neuroendocrine pathways involving the activity of gastrin, histamine, pituitary adenylate cyclase-activating peptide and acetylcholine. There are, therefore, several potential ways in which gastric acid secretion might be modified.<sup>1</sup> Targeting the muscarinic receptors through which acetylcholine stimulates gastric acid secretion is one possible approach, but muscarinic antagonists (e.g. atropine) are not specific to the gastrointestinal system and have adverse effects such as dry mouth and blurred vision. Competitive antagonists such as cimetidine and ranitidine can be used to block the binding of histamine to  $H_2$  receptors, but the parietal cell can still respond to other activating signals such as acetylcholine. Although histamine antagonists have reasonable efficacy at night, all patients quickly develop tolerance, perhaps as a result of upregulation of other pathways.<sup>1, 2</sup>

Given the redundancy inherent in the physiological control of gastric acid secretion, targeting the final effector in the secretion pathway – the gastric  $H^+/K^+$ -ATPase – is likely the most effective pharmacological approach. The potassium-competitive acid pump antagonists (APAs), which inhibit the gastric  $H^+K^+$ -

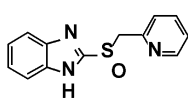
ATPase via  $K^+$ -competitive binding, are a promising new class of agent but their efficacy has yet to be demonstrated in clinical trials.<sup>3</sup> At present, proton pump inhibitors (PPIs) remain the most effective available therapy.

## EFFECTS OF DIFFERENT PPIs ON THE PARIETAL CELL

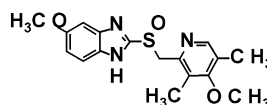
The benzimidazole derivative omeprazole was the first clinically useful PPI. Other benzimidazole PPIs subsequently introduced include lansoprazole, pantoprazole and rabeprazole. All these agents consist of two heterocyclic moieties – a pyridine and a benzimidazole moiety – linked via a methylsulfinyl group (Figure 1). A new PPI in development, tenatoprazole, has an imidazopyridine ring in place of the benzimidazole moiety (Figure 1).

Proton pump inhibitors are weak bases carried in the circulation and delivered to the parietal cell as prodrugs. In this form, PPIs are capable of crossing cell membranes. The parietal cell is the only membrane-enclosed space in the body with a pH below 4.0. In this acidic environment of pH  $\sim$ 1.0, PPIs accumulate in the secretory canaliculus of the parietal cell – at the luminal side of the gastric  $H^+K^+$ -ATPase – as a result of protonation of the pyridine moiety, which renders them less membrane permeable. It is likely that the monoprotonated species binds directly to the pump. Once on the acidic surface of the pump (or in the acid compartment), PPIs undergo a second protonation on the benzimidazole or imidazopyridine moiety that effects a chemical rearrangement involving

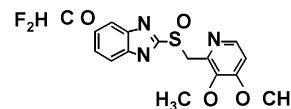
### Benzimidazoles



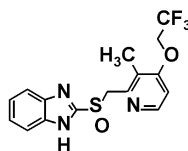
Timoprazole



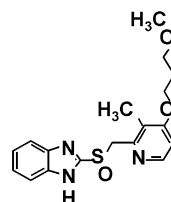
Omeprazole



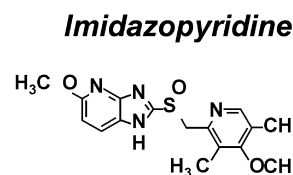
Pantoprazole



Lansoprazole



Rabeprazole



Tenatoprazole

Figure 1. Structures of proton pump inhibitors.

nucleophilic attack on the (unprotonated) pyridine by the now electrophilic 2C of the protonated benzimidazole, producing a planar cationic sulfenic acid.<sup>4, 5</sup> This thiophilic cation, or the sulfenamide form produced by dehydration of the sulfenic acid, is the active form of the drug that reacts with cysteine sulfhydryls on the pump to form one or more covalent disulphide bonds, thus inhibiting its activity. The need for these two protonation steps in the accumulation and activation of PPIs and the particular chemical requirements underlying them mean that the covalent reaction that inhibits the ATPase is specific to the active gastric H<sup>+</sup>K<sup>+</sup>-ATPase with a very large margin of safety given the pH of activation ( $\leq 2.0$ – $2.5$ ).<sup>5</sup>

### RATES OF ACTIVATION OF THE PPIs

Although all PPIs undergo acid accumulation and acid activation, and inhibit the H<sup>+</sup>K<sup>+</sup>-ATPase via covalent binding, there are some differences among them that may have clinical implications. The pK<sub>a</sub> for the first protonation leading to accumulation of PPIs in the parietal cell, pK<sub>a1</sub>, ranges among PPIs from 3.8 to 4.5 (Table 1);<sup>5</sup> the selective accumulation of PPIs in the parietal cell where the pH is below 4 relies on this pK<sub>a1</sub> of the pyridine ring. Substituents on a pyridine ring affect its tendency to undergo protonation and hence the level of protonation at a given pH. The substituents on the pyridine ring that influence the pK<sub>a1</sub> are similar among the PPIs, meaning that there is not a large range in pK<sub>a1</sub> values, but differences in the pK<sub>a1</sub> value among PPIs may have an effect on their activity.<sup>5</sup> For example, lansoprazole and rabeprazole have the same benzimidazole group, differing structurally only in the substituents on their pyridine rings (Figure 1). In such a situation, a higher pK<sub>a1</sub> (rabeprazole, 4.53) is associated with greater nucleophilicity

of the pyridine moiety and hence faster conversion to the active form of the drug.<sup>5</sup> However, when the benzimidazole moieties differ, the second step – protonation of the benzimidazole (or imidazopyridine in the case of tenatoprazole) – determines the rate of acid activation of a PPI in the parietal cell.<sup>5</sup> The pK<sub>a</sub> value for this step (pK<sub>a2</sub>) is  $\leq 1$  (Table 1), such that the reaction occurs rapidly in the acidic space of the parietal cell or on the surface of the active, acid-producing H<sup>+</sup>K<sup>+</sup>-ATPase (pH  $\sim 0.8$ ). A comparison of lansoprazole and pantoprazole serves to illustrate the influence of pK<sub>a2</sub> on the activation rate, as these two PPIs have a similar pK<sub>a1</sub> (3.83). The pK<sub>a2</sub> of lansoprazole (0.62) is higher than that of pantoprazole (0.11) (Table 1), meaning that the extent of benzimidazole protonation and hence the rate of activation of lansoprazole will be greater than that of pantoprazole. Although the pK<sub>a1</sub> does influence PPI activation, the maximum activation rate of current PPIs is generally dependent on the second protonation, pK<sub>a2</sub>, particularly in acidic conditions.<sup>5</sup> The selective accumulation of PPIs in the parietal cell (pK<sub>a1</sub>) and the requirement for acid activation (pK<sub>a2</sub>) ensure that covalent modification is specific to the active H<sup>+</sup>K<sup>+</sup>-ATPase in the highly acidic conditions generated when gastric acid secretion is stimulated. The pK<sub>a2</sub>, as the main determinant of the rate of activation, is also thought to affect the stability of inhibition of gastric acid secretion. All PPIs, when activated to the sulfenic acid form in conditions of proton transport by the H<sup>+</sup>K<sup>+</sup>-ATPase, react with the thiol residue on cysteine 813, a residue that is, according to crystallography and molecular modelling, exposed on the luminal surface of the pump in a vestibule.<sup>6–9</sup> Some PPIs additionally bind to other cysteine residues: lansoprazole to cysteine 321, omeprazole and esomeprazole (S-omeprazole) to cysteine 892, and pantoprazole and tenatoprazole to cysteine 822.<sup>1, 7, 8, 10–12</sup> Cysteines 321, 813 and 822 are in the proton-transport domain of the H<sup>+</sup>K<sup>+</sup>-ATPase, whereas cysteine 892 is on the external luminal surface, outside the transport domain, such that PPI binding to cysteine 892 does not affect the pump's proton-transporting capability.<sup>11, 13</sup> Cysteine 321 and 813 are in a luminal vestibule of the pump, accessible to reducing agents that can reverse the inhibition. Pantoprazole and tenatoprazole have two transport-inhibiting binding sites, cysteine 813 and cysteine 822. The latter, cysteine 822, in contrast to the more accessible cysteine 321 or 813, is located deep within the sixth transmembrane segment of the ATPase. It is thought

Table 1. pK<sub>a</sub> values of PPIs<sup>5</sup>

PPI	pK <sub>a1</sub>	pK <sub>a2</sub>
Omeprazole	4.06	0.79
Lansoprazole	3.83	0.62
Pantoprazole	3.83	0.11
Rabeprazole	4.53	0.62
Tenatoprazole	4.04	–0.12

PPI, proton pump inhibitor.

that when there is rapid acid activation, as with omeprazole, the PPI reacts rapidly with cysteine 813, preventing further entrance into the pump. With slow activation, such as that with pantoprazole or tenatoprazole, the pyridine-protonated species has the opportunity to additionally access cysteine 822 before the activating second protonation step.<sup>5</sup> These patterns of binding are consistent with the finding that omeprazole inhibition can be reversed with reducing agents that break disulphide bonds (glutathione, dithiothreitol) whereas the inhibitory activity of tenatoprazole and pantoprazole is stable in the presence of such agents (Figure 2), presumably because the cysteine residue at 822 to which these PPIs bind is less accessible to the reducing agents.<sup>1, 10, 12</sup>

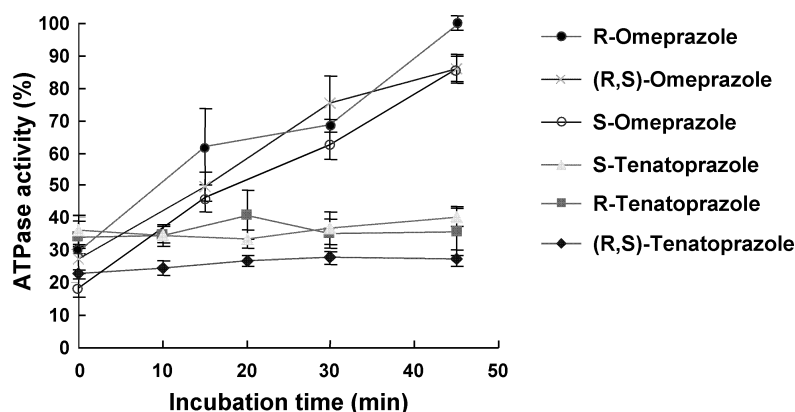
### PHARMACOKINETICS OF THE PPIs

Such differences in cysteine binding among the PPIs may, at least partly, underlie the differences among them in duration of inhibition of gastric acid secretion. Currently available benzimidazole-based PPIs have similar half-lives of 1–2 h.<sup>14–16</sup> However, their duration of effect is longer than would be expected simply on the basis of plasma half-life. Due to the possible instability of covalent binding to the proton pump, the inhibition of gastric acid secretion by PPIs is not maintained as long as would be predicted from the half-life of the H<sup>+</sup>K<sup>+</sup>-ATPase (about 54 h) and varies among PPIs.<sup>11</sup> Half-lives for the recovery of gastric acid secretion in humans range from less than 15 h for lansoprazole, through around 28 h for omeprazole, to around 46 h for pantoprazole.<sup>10, 17, 18</sup> The rate of recovery of gastric acid secretion following inhibition by PPIs depends on a combination of protein turnover (*de novo* synthesis of pump molecules), activation of

inactive pumps, and reactivation of inhibited pump molecules by endogenous reducing agents that break the covalent bond between the PPI and the pump allowing dissociation of the PPI. However, in the case of PPIs that bind to cysteine 822, which is inaccessible and resistant to reducing agents, recovery of acid secretion may depend entirely on production of new, active pump protein.<sup>10, 12</sup> Thus, PPIs that are accumulated and activated slowly, and bind to cysteine 822, will have a longer duration of acid inhibition. This may in principle influence their clinical effect, offering, for example, superior and sustained control of acid secretion at night.

Proton pump inhibitors are slow to achieve steady-state inhibition of gastric acid secretion, typically taking 3 days to achieve maximum acid suppression.<sup>1</sup> The slow onset of action of PPIs results from the continuous switching of inactive gastric acid pumps to the active state in conjunction with the requirement for PPI accumulation in the parietal cell and activation, coupled with the short plasma half-life of the PPIs.<sup>2, 18</sup> A PPI can inhibit only actively secreting pump molecules at the surface of the secretory canaliculus of the parietal cell; although any pumps with covalently bound PPI will remain inactive unless inhibition is reversed by a cellular reducing agent such as glutathione, pumps newly synthesized or activated after the plasma concentration of the PPI has fallen below threshold will not be inhibited. A short plasma half-life thus allows rapid restoration of gastric acid secretion by uninhibited, restored or new pumps, such that the extension of PPI half-life is an obvious goal; a PPI with a longer half-life should induce more prolonged blockade of proton pumps and is hence likely to bring about greater suppression of gastric acid secretion.<sup>18</sup> One approach to this has been to select

Figure 2. Stability of proton pump inhibitor inhibition of the gastric H<sup>+</sup>K<sup>+</sup>-ATPase. Inhibition by tenatoprazole remains stable in the presence of glutathione whereas ATPase activity returns rapidly with omeprazole as a result of reduction of the disulphide bond coupling omeprazole and the pump.



the enantiomeric form of a drug likely to undergo slower metabolism (e.g. S-omeprazole; esomeprazole).<sup>18, 19</sup> There is, however, no evidence that esomeprazole has clinical advantages over omeprazole at equivalent doses.<sup>20</sup> The imidazopyridine PPI tenatoprazole has a half-life of 7 h, which is considerably longer than that of the benzimidazole-based PPIs (Figure 3).<sup>21, 22</sup> This means that tenatoprazole, with a longer duration of action, has a theoretical advantage over benzimidazole-based PPIs, particularly with regard to night-time acid control.

### RELATING PPI PHARMACOKINETICS AND PHARMACODYNAMICS TO CLINICAL PERFORMANCE

As noted above, the elimination half-life for current PPIs is typically around 1–2 h. As these agents are usually prescribed once daily, this means that there is effectively no circulating PPI present at the end of the dosing interval. A PPI with an extended half-life might have a prolonged antisecretory effect with consequent therapeutic advantages.

Although current PPIs do not achieve a pharmacokinetic steady-state with conventional oral dosing, they do achieve a pharmacodynamic steady-state. Typically, the antisecretory effect progressively increases with the first few days of oral dosing. For any PPI, its area under the concentration/time curve (AUC) after oral dosing has proved to be the pharmacokinetic parameter that is the best predictor of antisecretory effect. PPIs with a more prolonged half-life would have a correspondingly higher AUC, which should translate into an enhanced antisecretory effect.

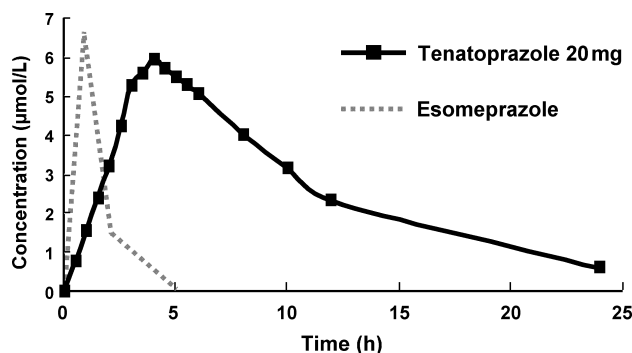


Figure 3. Residence time of proton pump inhibitors in blood.<sup>21, 22</sup>

There are different means whereby antisecretory effect can be described. Perhaps one of the most clinically useful is the duration of time during which a PPI maintains intragastric pH above certain thresholds. For example, the ability to maintain intragastric pH above 3 has been correlated with the healing of duodenal ulcer.<sup>23</sup> Maintenance of a pH above 4 has been correlated with the healing of both erosive oesophagitis<sup>24</sup> and gastric ulcer.<sup>25, 26</sup> In the management of patients with upper gastrointestinal bleeding from peptic ulcer disease, maintenance of an intragastric pH of at least 6 has been proposed to be optimal for prevention of clot disruption by acid-peptic activity. However, this has been a difficult target to reach with currently available PPIs, at least in healthy, *Helicobacter pylori*-negative individuals in western nations.<sup>27</sup>

### COMPARATIVE PHARMACOLOGY OF EXISTING PPIs: CLINICAL IMPLICATIONS

As discussed above, there are differences at the cellular level with respect to the rates with which conventional benzimidazole-based PPIs bind to – and dissociate from –  $H^+/K^+$ -ATPase, and the specific cysteines with which they bind. However, these observations have not been translated into clinically meaningful differences underscoring the impression that currently available PPIs are essentially interchangeable in clinical practice. Those PPIs given in doses that produce a demonstrably greater antisecretory effect are associated with minor advantages in clinical outcomes. For example, esomeprazole 40 mg has been found in some studies to produce slightly higher healing rates of erosive oesophagitis than omeprazole 20 mg<sup>28, 29</sup> or lansoprazole 30 mg.<sup>30</sup>

### IMPROVING THE PROFILES OF EXISTING PPIs

Apart from moving towards the top of the dose-response curve for the current PPIs, there are other potential approaches to enhancing their pharmacokinetic and pharmacodynamic properties. Administration of omeprazole in a fasting state as a non-enteric-coated formulation with a protective alkaline buffer has produced accelerated absorption and a more rapid onset of antisecretory effect than the corresponding conventional enteric-coated oral formulation.<sup>31, 32</sup> Newer PPIs that are not benzimidazole-based, such as tenatoprazole, have a markedly prolonged half-life

compared with existing PPIs; that has been associated with a more prolonged antisecretory effect, particularly during the night.<sup>22, 33, 34</sup> As PPIs generally exist as racemic mixtures, there may be some benefit to their administration as a purified preparation of the more biologically active isomer that undergoes less first-pass hepatic metabolism or has a more reliable pharmacodynamic profile. However, the overall degree of clinical improvement that could be expected from this may be limited unless the total dose is correspondingly increased. For example, although esomeprazole 40 mg has been shown in some trials to be superior to omeprazole 20 mg,<sup>28, 29</sup> there is no published evidence to indicate any advantage of esomeprazole 40 mg over omeprazole 40 mg.

## RECONSIDERING PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF PPIs THAT MAY PREDICT CLINICAL EFFICACY

As discussed, pharmacokinetics has been of very limited value in assessing the clinical efficacy of existing

PPIs. However, this may not be the case for newer agents. Tenatoprazole is currently unique among PPIs in that it is not benzimidazole-based and has a markedly prolonged half-life. This has been associated with a prolongation of useful antisecretory effect when compared with esomeprazole.<sup>22, 33, 34</sup> Therefore, half-life may be seen as a more important parameter for judging clinical efficacy. In the meantime, the pharmacodynamic effect of a PPI is still most usefully summarized as the proportion of time during which intragastric pH is maintained above particular threshold values.

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