Pharmacokinetics and Pharmacodynamics of the Proton Pump Inhibitors

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Proton pump inhibitor (PPI) is a prodrug which is activated by acid. Activated PPI binds covalently to the gastric H+\textsuperscript{+}, K+\textsuperscript{+} -ATPase via disulfide bond. Cys813 is the primary site responsible for the inhibition of acid pump enzyme, where PPIs bind. Omeprazole was the first PPI introduced in market, followed by pantoprazole, lansoprazole and rabeprazole. Though these PPIs share the core structures benzimidazole and pyridine, their pharmacokinetics and pharmacodynamics are a little different. Several factors must be considered in understanding the pharmacodynamics of PPIs, including: accumulation of PPI in the parietal cell, the proportion of the pump enzyme located at the canaliculus, de novo synthesis of new pump enzyme, metabolism of PPI, amounts of covalent binding of PPI in the parietal cell, and the stability of PPI binding. PPIs have about 1 hour of elimination half-life. Area under the plasmic concentration curve and the intragastric pH profile are very good indicators for evaluating PPI efficacy. Though CYP2C19 and CYP3A4 polymorphism are major components of PPI metabolism, the pharmacokinetics and pharmacodynamics of racemic mixture of PPIs depend on the CYP2C19 genotype status. S-omeprazole is relatively insensitive to CYP2C19, so better control of the intragastric pH is achieved. Similarly, R-lansoprazole was developed in order to increase the drug activity. Delayed-release formulation resulted in a longer duration of effective concentration of R-lansoprazole in blood, in addition to metabolic advantage. Thus, dexlansoprazole showed best control of the intragastric pH among the present PPIs. Overall, PPIs made significant progress in the management of acid-related diseases and improved health-related quality of life.

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Key Words
Area under the plasmic concentration curve; Hydrogen potassium ATPase; Gastric acid; Gastric endogenous activator protein, mammal; Pharmacokinetics; Pharmacology; Proton pump inhibitors

Introduction

Since the parietal cell was known to secrete gastric acid, many drugs were developed to target the parietal cell in order to inhibit the acid secretion. The major functional targets in the parietal cell were the histamine type 2 (H2) receptor and the gastric H+\textsuperscript{+}, K+\textsuperscript{+} -ATPase.1,2 Histamine binds to the H2 receptor, leading to elevation of intracellular cyclic AMP concentrations and activation of protein kinase A (PKA). One effect of PKA activation is the
phosphorylation of cytoskeletal proteins involved in the transport of the gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase from cytoplasm to the plasma membrane, i.e., from the vesicular and/or tubular vesicular membrane to the canaliculus. In the canaliculus, the gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase can access \( \text{KCl} \) of the extracellular region and exchange the intracellular proton with the extracellular \( \text{K} \) ion, which represents the gastric acid secretion. The \( \text{H}2 \) receptor is crucial in making the acid secreting morphology of the parietal cell, while the gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase is the final functional work on the acid secretion.

The \( \text{H}2 \) receptor antagonist was first introduced in 1977\(^{1,3} \) and dramatically increased the healing rates of peptic ulcer disease. The receptor antagonist, however, showed limited healing effects on the gastroesophageal reflux disease (GERD) since the antagonist provided limited pH control in the stomach. In order to get better pH control in the stomach, the acid secreting enzyme was considered as a drug target. The proton pump inhibitor (PPI), introduced in 1989, targeted the gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase and reflected a major medical therapeutic breakthrough in the treatment of peptic ulcers and GERD, resulting in more rapid healing of the lesions and symptom relief.

PPI is a prodrug which is activated by acid. PPI inhibits the gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase by covalent bonding at cysteines near the ion pathway. Due to the property of covalent bonds, the inhibitory activity lasts longer.

### Structure of the Gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase

The gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase is an \( \alpha \), \( \beta \)-heterodimeric enzyme. The \( \alpha \) subunit, with molecular mass of about 100 kDa, has the catalytic site and the \( \beta \) subunit, with peptide mass of 35 kDa, is strongly but non-covalently associated with the \( \alpha \) subunit.

The gastric \( \alpha \) subunit has conserved sequences along with the other P\(_2\) type ATPases, the sarcoplasmic reticulum \( \text{Ca}^{2+} \)-ATPase and the \( \text{Na}^+ \), \( \text{K}^+ \)-ATPase, for the ATP binding site and the phosphorylation site. The phosphorylation site was observed to be at Asp386,\(^{4} \) which is well conserved in other P\(_2\) type ATPases. The membrane topology of the \( \alpha \) subunit has been shown to contain 10 membrane spanning segments.\(^{5-7} \) The \( \beta \) subunit consists of about 290 amino acids with a single transmembrane segment, which is located at the region near the N-terminus. There are 3 disulfide bridges in the luminal region of the \( \beta \) subunit.\(^{6,8} \) Six and seven putative N-glycosylated sites (AsnXaaSer and AsnXaaThr) are found in pig and rabbit, respectively.\(^{10-12} \) Seven N-glycosylated sites of the gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase \( \beta \) subunit are conserved in rat and human.

The \( \alpha \) subunit of the \( \text{H}^+ \), \( \text{K}^+ \)-ATPase is strongly associated with the \( \beta \) subunit.\(^{13} \) The region of the sequence Arg898 to Arg922 in the \( \alpha \) subunit was known to have strong interactions with the extracytoplasmic domain of the \( \beta \) subunit. In the plasma membrane, the gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase may function as an (\( \alpha \)-\( \beta \))-dimeric heterodimer.\(^{14} \) The important observation was that the membrane preparation showed full stoichiometry with respect to ATP binding (1 mol/mol of \( \alpha \)-\( \beta \)) and half stoichiometry with respect to inhibitor binding and phosphorylation, suggesting an (\( \alpha \)-\( \beta \))\(_2\) oligomer.

The \( \text{H}^+ \), \( \text{K}^+ \)-ATPase \( \alpha \)-subunit is composed of 10 transmembrane helices (TM1 through TM10) and 3 cytosolic domains: N (nucleotide binding), P (phosphorylation) and A (activation) (Fig. 1). Recently, 2 dimensional crystals of the \( \text{H}^+ \), \( \text{K}^+ \)-ATPase were analyzed in the presence of the phosphate analog BeF and an inhibitor SCH28080.\(^{15,16} \) This structure of the E\(_2\)P conformation was similar to that of Ca\(^{2+} \)-ATPase. The overall structure shows characteristic features of the ADP-insensitive E\(_2\)P conformation, to which SCH28080 is preferentially bound. The BeF-bound phosphorylation site (Asp386) at the P domain is covered by the A domain, and the ADP-bound N domain is separated from the P domain, thus the bound phosphate analog seems to be isolated from both ADP and the bulk solution.

![Figure 1. A model structure of the gastric \( \text{H}^+ \), \( \text{K}^+ \)-ATPase.](image-url)