

# Pharmacology and Biochemistry

## Discussion I

### (Small Group)

#### OBJECTIVES

- Determine if a drug is a weak acid or weak base based on its ionizable groups.
- Calculate the fractions of a drug that are charged and uncharged in body compartments of differing pH, based upon the drug's pKa and acidic or basic nature.
- Describe the normal gradients of Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Cl<sup>-</sup> that exist between the intracellular and extracellular fluid of eukaryotic cells. Describe how these gradients are maintained and used to power transport across membranes in different cell types.
- Apply the concepts presented in the lectures titled "Introduction to Pharmacology," and "Diffusion and Transport Across Cell Membranes" to explain transport and absorption characteristics of omeprazole.

#### KEY WORDS

active transport

antiport

cotransporter

electrochemical gradient

Henderson-Hasselbach equation

membrane transport protein

passive transport

pKa

weak acid

weak base

#### INTRODUCTION

The purpose of this small group is to expand on and reinforce the concepts presented in the lectures titled "Introduction to Pharmacology," and "Diffusion and Transport Across Cell Membranes."

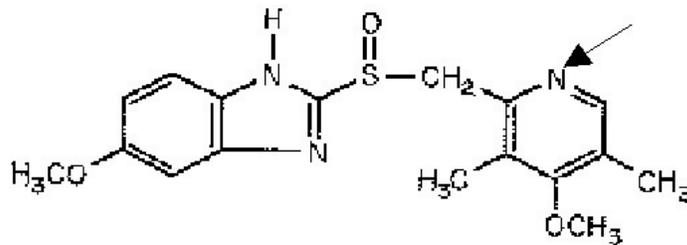
#### Before coming to class you should:

- Read the syllabus sections for those lectures, and complete the reading required for the Introduction to Pharmacology in Katzung's *Basic and Clinical Pharmacology*.
- Look up the pH of the fluids in the following locations: blood, stomach, small intestine, urine, breast milk, prostatic secretions (available in Table 1-2 of Katzung's *Basic and Clinical Pharmacology*).
- Read through the tasks described below, gather the information you think you'll need to complete the tasks and begin to formulate answers to the questions. You may be assigned by your small group leader to complete one of the tasks ahead of time and lead your small group through that problem in the discussion. Other problems are to be solved in the small group. Details will be announced in class.

**Task 1:** Drugs that inhibit the secretion of stomach acid are amongst the most widely used drugs in the world. These drugs are used to treat and prevent two common disorders: gastrointestinal ulcers and gastroesophageal reflux disease (GERD, characterized by frequent heartburn and regurgitation). An example of such a drug is omeprazole. Omeprazole (Prilosec) is administered orally in capsules that release the drug in the duodenum.

Omeprazole has two ionizable groups, a pyridine and a benzimidazole group. When ionized at the pyridine (arrow in Figure 1), omeprazole has a pKa of 4.

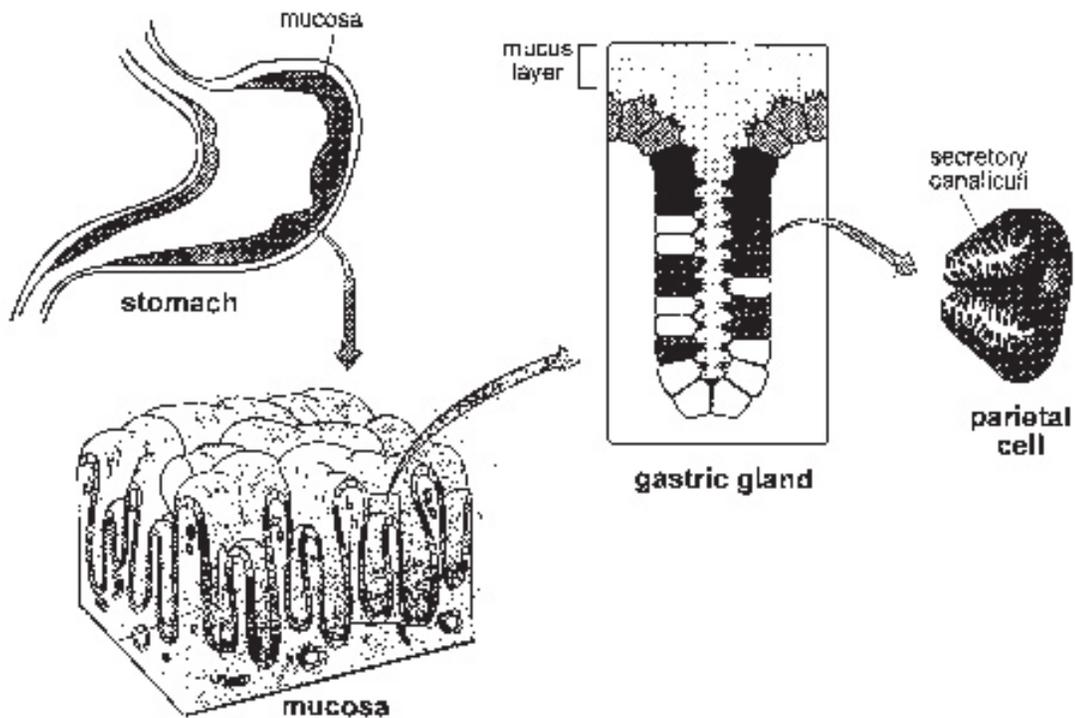
- Draw the chemical structure of the form of omeprazole that contains an ionized pyridine group. Is omeprazole a weak acid or a weak base? Estimate its molecular weight.
- If the drug were delivered in an un-encapsulated form, would the drug be more readily absorbed in the stomach or the small intestine? Why?



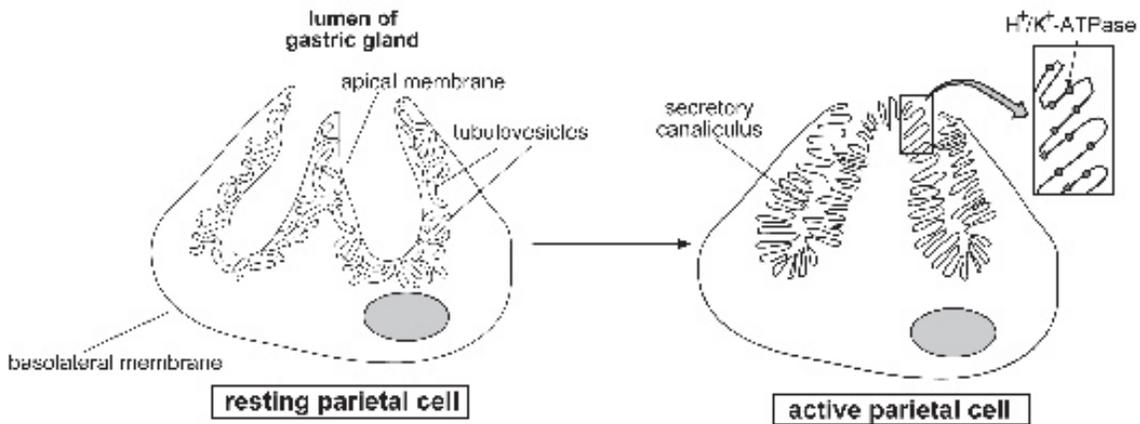
**Figure 1:** Structure of the neutral form of omeprazole. The arrow indicates the ionizable nitrogen in the pyridine group.

**Task 2:** The target of omeprazole is an ATP-driven  $H^+/K^+$ -ATPase, an integral plasma membrane protein. This  $H^+/K^+$ -ATPase is located in parietal cells, specialized secretory cells situated in the epithelium of glands in the mucosa of the stomach (Figure 2). The key function of parietal cells is secretion of acid (HCl) into the lumen of the stomach. The parietal cell has two states, resting (in which acid is not being actively secreted) and active (acid secreting) (Figure 3). In a parietal cell that is actively secreting acid, the  $H^+/K^+$ -ATPase is located on the apical side of the cell within a portion of the plasma membrane that forms a structure known as the secretory canaliculus. The  $H^+/K^+$ -ATPase in the canaliculus transports  $K^+$  against its normal electrochemical gradient.

- Diagram a parietal cell and indicate the normal gradients for  $Na^+$ ,  $Cl^-$ ,  $K^+$  and  $Ca^{2+}$  across the apical and basolateral membranes.
- Add the  $H^+/K^+$ -ATPase to the drawing and diagram the directions in which the pump moves ions. Relate the function of the  $H^+/K^+$ -ATPase to the function of the cell.



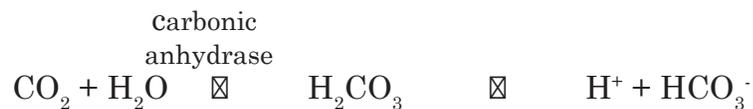
**Figure 2: The gastric gland of the stomach.** *The gastric gland is made up of several cell types, including parietal cells, which are typically found in the neck and base of the gland. A mucus gel secreted by epithelial cells coats and protects the surface of the stomach.*



**Figure 3: Resting vs. active parietal cell.** *Between meals, parietal cells sequester the  $H^+/K^+$ -ATPase in an internal tubulovesicular membrane system. Stimulation by gastrin, histamine, or acetylcholine (all released during digestion), results in a cytoskeletal rearrangement in which the tubulovesicular membranes fuse with the plasma membrane, forming the secretory canaliculi. This event exposes the pump to the lumen of the gastric gland.*

**Task 3:** Omeprazole inhibits its target by covalently attaching to a cysteine residue located in the extracellular domain of the target protein. The pH of the lumen of the secretory canaliculus is 1. Calculate the **ratio at steady state** of the concentration of the drug in the secretory canaliculus to the concentration in the blood. What implications does the pH difference between the blood and the secretory canaliculus have for the action of the drug?

**Task 4:** In addition to the ATP-driven  $H^+/K^+$  ATPase, the apical membrane of the secretory canaliculus contains  $K^+$  channels and  $Cl^-$  channels. The basolateral membrane of the parietal cell contains a  $Cl^-/HCO_3^-$  antiporter. The cell's principal source of protons is a reaction catalyzed by an enzyme called carbonic anhydrase (shown below). The activity of carbonic anhydrase increases during digestion because  $CO_2$  builds up as a metabolic by-product in the cells.



Chemical mediators present during the digestion of a meal cause the  $K^+$  and  $Cl^-$  channels to open. Putting all of this together, explain how the parietal cell pumps HCl into the stomach. What is the driving force for the movement of chloride ions into the stomach?