Design and use of a proton pump inhibitor case to integrate physiology, pharmacology, and biochemistry

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Submitted 12 September 2013; accepted in final form 2 December 2013

The use of drugs to integrate basic and clinical sciences is frequently used in a lecture format, but the availability of alternative pedagogical approaches that address higher-order learning are not widely available. The use of case studies and case-based projects to reinforce lectures can help link basic and clinical disciplines and promote knowledge retention (2). Case-based projects also help students with varying levels of background education see the applicability of topic material, and this may maintain engagement (5, 6). However, both the significant time and effort and the general breadth of knowledge across basic science content areas necessary to construct clinically relevant basic science cases may serve as hindrances to their development.

To address this issue, over the course of ~2 mo, I designed an integrated case that uses proton pump inhibitors (PPIs) to connect basic pharmacological principles with basic gastrointestinal physiology and pathophysiology. The development of this case grew out of discussions with clinical faculty members and students regarding general confusion surrounding how and why drugs that act in the stomach on parietal cells are made as enterically coated prodrugs to protect them from destruction by stomach acid. Thus, in the process of searching the literature to resolve this paradox, it became apparent that this would be an excellent way to connect gastrointestinal physiology, pharmacology, and biochemistry (1).

The first iteration of this case is presented in the first module of our curriculum (Fig. 1). This module covers basic biochemistry, cell biology, genetics, and pharmacological principles over the course of 8 wk. As part of this module, students are introduced to receptors and channels followed by lectures on pharmacokinetic principles including information on drug absorption, distribution, metabolism, and excretion. In these sessions, we discuss the principle of ion trapping, and this serves as the segue to the case. Normal anatomy and physiology content, including gastrointestinal physiology, is presented in the subsequent module. Thus, the case introduces students to the principles of gastric acid secretion and buffering in an applied manner together with pharmacology before their formal presentation in a physiological context in the second module. When the cases are administered, students work on the case first as individuals before assembling in groups, which consist of eight members. By doing this, students are afforded the opportunity for individual thought and expression without the pressures of a group. Upon the completion of the session, I collect both the individual answers and group answers for comparison. This is followed by a detailed discussion on the concepts addressed in the learning objectives and the answers to the questions.

The PPI case is represented to students in the second year of the curriculum, when they cover gastrointestinal pathophysiology in the gastrointestinal, hepatic, and renal systems module. In this module, students must work through the same case with new questions on gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) along with old questions related to gastrointestinal physiology and pharmacological principles. In this way, new material can be linked with previously learned material with an increase in difficulty level, similar to what is done in a spiral curriculum (4).

The first part of the case provides a background on PPIs and parietal cells. Included with the background are learning objectives and two figures that help students visualize the location of $\text{H}^+\cdot\text{K}^+\cdot\text{ATPase}$ on a parietal cell and the general structure of a PPI so that they can appreciate the concept of prodrug design.

**Background**

PPIs, such as omeprazole, are frequently used to reduce acid production, for example, in individuals with GERD and PUD. Each of the agents in this class share the general structure (Fig. 2) of a benzimidazole group linked to a pyridine group via a sulfoxide moiety. These agents are prodrugs and, as such, are inactive in their native form. In the case of PPIs, exposure to low pH results in a chemical rearrangement that unmasks the highly reactive sulfur atom. This, in turn, allows the PPI to covalently bind to $\text{H}^+\cdot\text{K}^+\cdot\text{ATPase}$ on the surface of gastric parietal cells and inhibit the extrusion of $\text{H}^+$ into the stomach lumen (Fig. 3). Due to the fact that PPIs are acid labile (easily destroyed by acid), the oral dosage form must be enteric coated to protect them from degradation in the stomach. Alternatively, as a means to bypass the harsh acidic environment of the stomach, PPIs may be administered intravenously.

After reviewing the background, the student is directed to the actual clinical case.

**The Case**

G.S. is a 45-yr-old, 6-ft-tall, 223-lb man who smokes a pack of cigarettes a day. He presents to the Emergency Department complaining of a burning sensation in both his chest and his abdominal region and persistent diarrhea. An upper gastrointestinal radiological series reveals the presence of a duodenal ulcer, which is confirmed by endoscopy. A blood antibody test confirms the presence of infectious *Helicobacter pylori* in this patient. Combination therapy consisting of omeprazole (20 mg) and amoxicillin (1 g) is initiated for once a day for 5 days, followed by omeprazole (20 mg) and clarithromycin (500 mg) twice a day for 10 days.

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Students are allotted 15 min to read the case and background individually. The learning objectives for the first iteration of the case as well as the questions that students are instructed to answer are shown below. The first set of questions was designed to address basic pharmacology content as it relates to drug formulation, ion trapping, the role of the acid-base balance in drug distribution, and types of bonding in drug-receptor interactions.

First Iteration of the Case

Learning objectives. The learning objectives for the first iteration of the case are as follows:

1. Outline how the principles of ion trapping govern the diffusion of weak acids and bases across biological membranes.
2. Describe the role that ion channels and pumps play in the regulation of gastric acid secretion.
3. Compare the pH differences between the stomach, duodenum, plasma, parietal cell, and canaliculus.
4. Explain why PPIs have longer-lasting acid suppression than histamine H₂ blockers.

Questions. The questions for the first iteration of the case are as follows:

1. If the oral dosage form is enteric coated, then why is it necessary for PPIs to be synthesized as prodrugs?
2. In general, PPIs, as a class, are weak bases. Based on this information, where would you predict that PPIs are absorbed?
3. How does the PPI reach its site of action?
4. What is ion trapping and how might this concept be relevant to the mechanism of action of PPIs?
5. What effect would a covalent interaction between a PPI and H⁺-K⁺-ATPase have on the duration of action of the PPI?

Second Iteration of the Case

Learning objectives. The learning objectives for the second iteration of the case are as follows:

1. Outline the signaling pathways and mediators which regulate parietal cell function.
2. Explain the etiology and symptoms of GERD and PUD.
3. List and discuss the major adverse events associated with PPI administration.
4. Outline how the principles of ion trapping govern the diffusion of weak acids and bases across biological membranes.
5. Describe the role that ion channels and pumps play in the regulation of gastric acid secretion.
6. Compare the pH differences between the stomach, duodenum, plasma, parietal cell, and canaliculus.
7. Explain why PPIs have longer-lasting acid suppression than histamine H₂ blockers.

Questions. The questions for the second iteration of the case are as follows:

1. Where is gastrin produced and how is gastrin production regulated?
2. What effect would inhibition of prostaglandin production have on mucus production in the stomach?
3. How does acid-base balance in the gastrointestinal tract change during fed and fasting states?
4. How do changes in gastric acid concentrations affect acetylcholine, gastrin, and histamine release and signaling?
5. What is ion trapping and how might this concept be relevant to the mechanism of action of PPIs?

After the completion of the questions as individuals, students are instructed to assemble into their predetermined groups, where they go over the questions again and compare the rationale for their respective answers. After the groups are finished and they turn in their answers, I hold a brief wrap-up discussion on the case and answers to cement learning.

Discussion and Summary

The development of meaningful and relevant cases that connect topics across multiple disciplines is a viable avenue to facilitate student learning and aid in information retention. Indeed, the retention of basic science content in the medical curriculum remains a common problem, and many medical schools have explored ways to bring back basic content in the curriculum to improve retention (3, 7). In an effort to link physiology and pharmacology together in a vertical fashion, a case study was designed using the mechanism of action of PPIs and GERD as a unifying element. This case was used in two different modules over the course of 2 yr at a United States medical school. In the first module, the intent was to use a clinically relevant case study to highlight the importance of drug delivery, ion trapping, formulation, and drug-receptor interactions with gastrointestinal physiology. In the second module, the goal was to use the same case to highlight and review key aspects of gastric acid secretion and regulation. Additionally, by including questions from the previous year, the students were encouraged to recall basic pharmacological principles. Students had to work on the case alone at first and struggle with the questions and problems presented before meeting in groups. Once students assembled into groups, peer learning ensued as they discussed, meshed, and modified their individual answers to the questions. Based on classroom observations and student comments, it was apparent that students enjoyed the challenge of working on this case and especially liked having an opportunity to work as individuals before assembling into groups. Once students assembled into groups, they were engaged and, in most cases, were able to answer the questions clearly. They also appreciated the wrap-up discussion at the end of the session. Future studies are planned for the formal assessment of learning outcomes.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.W.L. conception and design of research; M.W.L. prepared figures; M.W.L. drafted manuscript; M.W.L. edited and revised manuscript; M.W.L. approved final version of manuscript.

REFERENCES


Fig. 3. Anatomy of a parietal cell. The principal target of PPIs is H+-K+-ATPase. Key regulatory points governed by acetylcholine (ACh), gastrin (G), and histamine (H) are also noted. M3, muscarinic ACh receptor; H2, histamine H2 receptor; CCK2, cholecystokinin receptor; ECL, cell, enterochromaffin-like cell.

