Proton Pump Inhibitors: Use in Pediatric Patients

The Centers for Medicare & Medicaid Services (CMS) Medicaid Integrity Group (MIG) has identified issues with using medications in the proton pump inhibitor (PPI) drug therapy class. The U.S. Food and Drug Administration (FDA) approves product labeling for prescription drugs. The MIG has identified that some providers may have prescribed PPIs outside of FDA-approved product labeling for indication, age, dosage, or duration of therapy. Therefore, CMS wants to improve quality of care and enhance patient safety by educating providers on the proper use of PPIs in pediatric patients.

This fact sheet summarizes the current FDA-approved product labeling for the use of PPI medications in pediatric patients. After reading this fact sheet, providers should be able to accurately:

- Recall whether each PPI is FDA-approved to treat gastroesophageal reflux disease (GERD), erosive esophagitis (EE), or both conditions in pediatric patients;
- Recall the dosing options and guidelines for each PPI that is FDA approved for pediatric patients;
- Explain why some PPIs are not indicated for use in infants; and
- Describe the adverse reactions of, and risks related to, the use of PPIs in pediatric patients.

Defining Pediatric Patients

For the purpose of this document, the term "pediatric patients" collectively includes infants, children, and adolescents younger than 18 years old. Infants are further defined to be any patient younger than 1 year old.

The literature on PPIs does not have well-defined age ranges for pediatric patients. Some studies define children as patients 1 to 12 years old and adolescents as patients 13 to 17 years old. Other studies define children as patients 1 to 17 years old. The ages of the patients were also inconsistent in the clinical trials conducted for medication approval. This inconsistency is reflected in the age ranges in Figure 1.

Overview of Proton Pump Inhibitors

PPIs block the acid-producing enzyme system in the stomach wall and prevent acid production in the stomach. Lack of acid in the stomach prevents ulcer formation; promotes healing of existing ulcers in the esophagus, stomach, and duodenum; and provides symptom relief. PPIs differ in how they are metabolized by the body, how they interact with other medications, and the length of time they are active in the body. However, there is no evidence that one PPI is more effective than another at treating any of the approved indications.

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FDA-Approved Indications for Proton Pump Inhibitors in Pediatric Patients

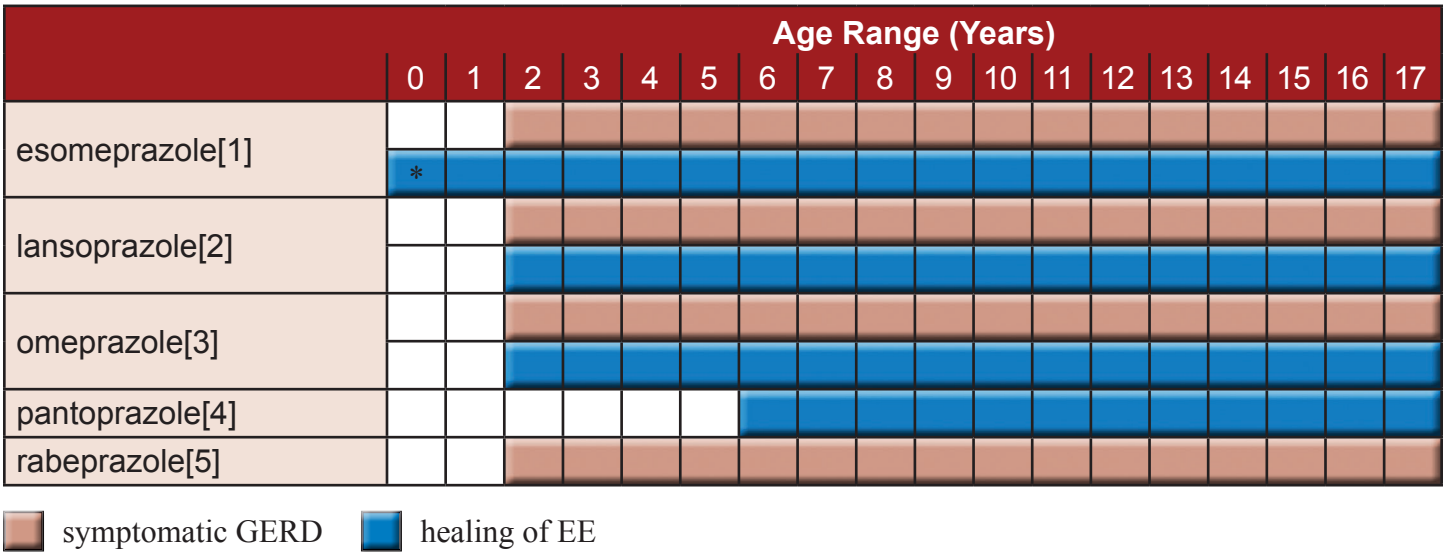
Medications in the PPI drug therapy class have been proven safe and effective in children and adolescents for the short-term treatment of GERD and EE. However, PPIs are often used to treat conditions that have not been formally diagnosed.

PPIs are used to prevent and treat gastric acid-related conditions. These FDA-approved indications and age ranges apply to PPI prescriptions:

- The FDA-approved indications for use in pediatric patients are the short-term treatment of symptomatic GERD and healing of EE;
- Pantoprazole is the only PPI approved for pediatric use that is not approved for use in children younger than 5 years old;
- Only esomeprazole is FDA-approved for patients younger than 1 year old; and
- Five of the currently available prescription PPIs have an FDA-approved indication for patients younger than 18 years old; no over-the-counter (OTC) PPIs are approved for patients younger than 18 years old.

Figure 1 provides the FDA-approved pediatric age ranges and indications for PPIs. The FDA-approved pediatric indications and dosages for medications in the PPI drug therapy class are provided in the document "Proton Pump Inhibitors: U.S. Food and Drug Administration-Approved Indications and Dosages for Pediatric Patients" available at https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/protonpump-education.html on the CMS website.

Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Proton Pump Inhibitors



* Treatment may begin as early as 1 month of age for this indication.

Treatment Guidelines for Children with Gastroesophageal Reflux Disease

The Agency for Healthcare Research and Quality (AHRQ) hosts a database of treatment guidelines. The AHRQ is a branch of the U.S. Department of Health and Human Services. For information on the available treatment guidelines, search "proton pump inhibitors" or any of the gastric acid-related conditions for which a PPI is an indicated treatment in the AHRQ's National Guideline Clearinghouse at https://www.guideline.gov on the Internet.

ACRONYMS

AHRQ	Agency for Healthcare Research and Quality
CDAD	Clostridium difficile-associated diarrhea
CDER	Center for Drug Evaluation and Research
CgA	Chromogranin
CMS	Centers for Medicare & Medicaid Services
EE	erosive esophagitis
FDA	U.S. Food and Drug Administration
GERD	gastroesophageal reflux disease
MIG	Medicaid Integrity Group
MPIE	Medicaid Program Integrity Education
OTC	over the counter
PPI	proton pump inhibitor

Clinical Trials for the Treatment of Gastroesophageal Reflux Disease in Infants

Clinical trials for the use of PPIs in infants have been conducted with esomeprazole, lansoprazole, and pantoprazole. The results of these trials showed that PPIs are not effective in patients younger than 1 year old for the treatment of symptomatic GERD. However, esomeprazole has recently been shown to be safe and effective for treating erosive esophagitis caused by acid-mediated GERD in pediatric patients 1 month old through less than 1 year old.[6]

Infants treated with lansoprazole for symptoms of crying, fussing, or irritability with feedings showed no difference in the percentage of response than patients treated with a placebo. This lack of efficacy does not support the use of lansoprazole in infants.[7]

Pantoprazole was studied in 129 patients (1 to 11 months old) with symptomatic GERD. This multicenter, randomized, double-blind, placebo-controlled treatment-withdrawal study found that pantoprazole was not effective. Adverse reactions were more prevalent in the patients who received pantoprazole.[8]

Adverse Reactions and Risks of the Use of Proton Pump Inhibitors in Pediatric Patients

PPIs are generally well tolerated. The most common adverse reactions seen in pediatric patients are headache, diarrhea, constipation, and nausea.[9, 10, 11, 12, 13] The use of PPIs has been associated with drug interactions and *Clostridium difficile*-associated diarrhea (CDAD). Omeprazole and esomeprazole have been associated with false positive results in diagnostic investigations for neuroendocrine tumors. Hypomagnesemia with PPIs has been reported in adults.

Risk of Drug Interactions with Proton Pump Inhibitors

Clinically significant drug interactions with PPIs are rare. Chronic acid suppression can minimize the effectiveness of any medication requiring an acidic environment for absorption. Commonly prescribed medications affected by acid suppression are ampicillin esters, digoxin, erlotinib, atazanavir, ketoconazole, and iron salts.[14]

Adverse drug interactions may also occur between PPIs and other medications that are metabolized via the cytochrome P450 system. While specific interactions are not well documented, there is substantial evidence regarding an interaction between clopidogrel and omeprazole.[15] Other drug interactions that may be clinically significant are dependent on the specific cytochrome P450 enzyme substrates and the specific PPI. Search the medication name at https://www.accessdata.fda.gov/scripts/cder/drugsatfda on the FDA website to retrieve prescribing information and detailed drug interactions for each PPI medication.

Risk of *Clostridium difficile*-Associated Diarrhea

On February 8, 2012, the FDA published a Drug Safety Communication to inform patients, caregivers, and providers that PPIs may be associated with an increased risk of CDAD. Symptoms of CDAD include abdominal pain, fever, and watery stools. Patients who take a PPI and develop diarrhea that does not improve should be evaluated for CDAD. Patients with advanced age, certain chronic medical conditions, and those taking broad spectrum antibiotics are at greatest risk for developing CDAD. The FDA recommends using the lowest dose and shortest duration of PPI therapy possible and recommends advising patients to seek medical attention if they develop symptoms of CDAD.[16] The FDA requires that a Medication Guide be dispensed with every new or refilled PPI prescription. The Medication Guide informs patients, caregivers, and providers about the risk of CDAD when taking a PPI. Links to the Medication Guides can be found at http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm on the FDA website.

Omeprazole Interactions with Diagnostic Investigations for Neuroendocrine Tumors

Using omeprazole or esomeprazole may cause Chromogranin A (CgA) levels to increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. In March 2014, the FDA published a Drug Safety Communication to inform health care providers to temporarily stop omeprazole treatment at least 14 days prior to assessing CgA levels and consider retesting if the initial CgA levels are high. The FDA recommends using the same commercial laboratory for testing if serial tests are performed because reference ranges between tests may vary.[17, 18]

Risk of Hypomagnesemia

In March 2011, the FDA published a Drug Safety Communication to inform consumers and health professionals that the long-term use of PPIs may cause hypomagnesemia. In 25 percent of patients, magnesium supplementation was not sufficient to correct PPI-induced hypomagnesemia; rather, PPI therapy had to be discontinued. The deficiency did not appear to be dose-related and reappeared after rechallenge with a PPI. The FDA recommends obtaining a serum magnesium level prior to initiation of therapy if a patient is to be on prolonged treatment.[19]

Acute Interstitial Nephritis

During PPI therapy patients may develop a hypersensitivity reaction that leads to acute interstitial nephritis. Interstitial nephritis can cause kidney problems, including acute kidney failure. In about half of the cases, decreased urine output is one of the symptoms, although others may experience increased urine output. Other symptoms may include blood in the urine, fever, mental status changes, nausea, swelling, and weight gain.[20] Discontinue PPI therapy if acute interstitial nephritis is diagnosed.[21]

Cyanocobalamin (Vitamin B-12) Deficiency

Daily therapy with any acid-suppressing medications for 3 years or more may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Symptoms may include anemia, loss of balance, numbness or tingling in the arms and legs, and weakness.[22] Reports of this deficiency are rare, but consider this diagnosis if symptoms warrant.[23]

Resources

Visit http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-State/By-State.html for links to State Medicaid program websites.

The Center for Drug Evaluation and Research (CDER) hosts a website providing health professionals with current information on OTC and prescription drugs. Visit http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals to access drug-related databases and current information on drug recalls and alerts, new and generic drug approvals, and drug safety and availability.

Section 1927(g)(1)(B) of the Social Security Act identifies the predetermined standards that the State's drug use review program must use to assess data on drug use. Visit http://www.ssa.gov/OP_Home/ssact/title19/1927.htm for information on the compendia.

To see the electronic version of this fact sheet and the other products included in the "Proton Pump Inhibitors" Toolkit, visit the Medicaid Program Integrity Education page at https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/pharmacy-ed-materials.html on the CMS website.

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