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PPI

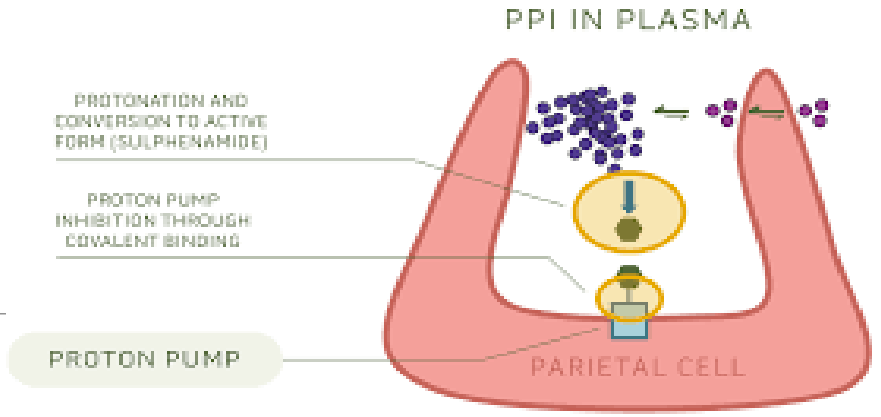
Inhibit gastric acid production through irreversible binding to the gastric parietal cell HR/KR ATPase pump (the ‘‘proton pump)

The primary indication is the treatment of peptic acid related diseases.

The last 20 years or so, however, have seen a significant rise in their

utilization, especially in infants

MECHANISMS OF ACTION



The basic mechanism of action is essentially the same

PPIs can be regarded as prodrugs, which are converted into active forms when the nitrogen on the pyridine group is protonated, resulting in the formation of a permanent cation.

PPIs are minimally protonated at neutral pH, and maximally protonated in greatly acidic environment of the intracellular canaliculi of parietal cells in the stomach.

Once covalently bound, the Hþ/Kþ ATPase enzyme becomes nonfunctional and activity only returns by parietal cell synthesis of new Hþ/Kþ ATPase molecules

For oral administration, PPIs should be enteric-coated to prevent premature protonation in the acidic environment in the stomach in order to enable delivery of the intact drug into the duodenum.

There they are rapidly absorbed, and plasma concentration reaches a 1–3 hours after ingestion

PPIs are metabolized to inactive metabolites in the liver by cytochrome P450

The degree of metabolism metabolic clearance of PPIs is slower in neonates faster in infants and young children and comparable with adults in the older

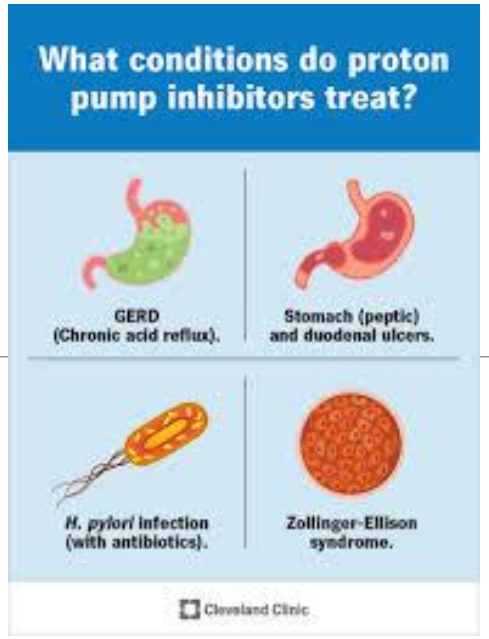
PPIs have direct anti-inflammatory mechanism of action.

They inhibit eotaxin-3 expression by esophageal epithelial cells

Effective in treatment of EOE

GERD

Indication & Efficacy



Peptic acid related diseases,

GERD

peptic ulcer disease

hyper- secretory states (Zollinger-Ellison syndrome),

EoE

Helicobacter pylori infection

SAFETY

Adverse events with PPI therapy appear in up to 34% of cases,

- headaches, (mild – moderate)
- diarrhea
- nausea
- abdominal pain
- constipation

Increase the risk for more serious adverse events:

- necrotizing enterocolitis (NEC) in premature infants
- nosocomial infections
- hepatic toxicity (several cases of adult)
- interstitial nephritis (rare – idiosyncratic)

bacteremia/sepsis,

association with ventilator-associated pneumonia is conflicting

acute gastroenteritis

community-acquired pneumonia

lower respiratory tract infections

upper respiratory tract infections and bronchiolitis

community-acquired pneumonia (both ranitidine and PPI)

in children with poor asthma control, more respiratory infections

Long-Term Safety

Prolonged hypochlorhydria may lead to gastric bacterial overgrowth, as noted in adults and neonates.

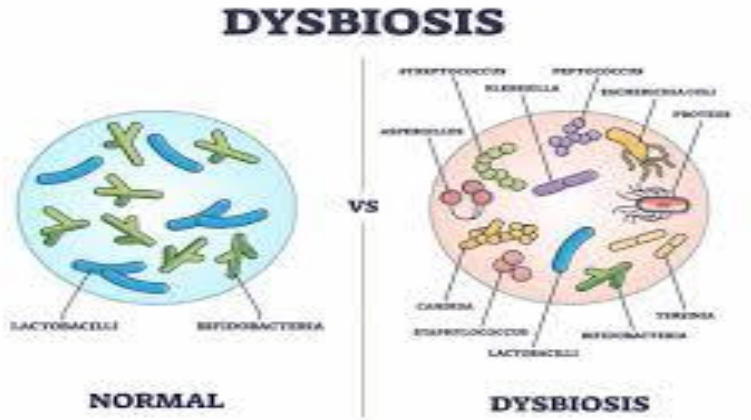
Increase susceptibility to bacterial entero pathogens

Salmonella infection,

Campylobacter

Clostridium difficile

Acute G/E



Intestinal dysbiosis.

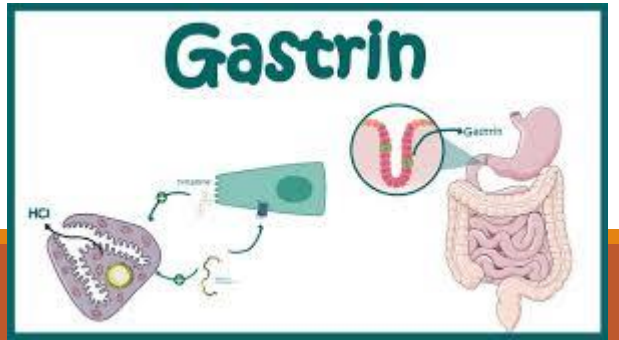
-Significant increase of Streptococcaceae and Enterococcaceae which are risk factors for Clostridium difficile infection

- Decrease of Faecalibacterium, a commensal anti- inflammatory microorganism, were observed secondary to PPI therapy.

Increased gastrin levels (two-to fivefold rise in half of the treated patients).

This leads to stimulation of enterochromaffin-like cell

Carcinoid tumors are observed in animals treated lifelong with high-dose omeprazole or an H2 receptor antagonist. Although enterochromaffin-like hyperplasia has been observed in adults, carcinoid tumor reported only once in an adult.



Inflammatory fundic polyps and nodules : in children receiving PPI (omeprazole) for more than six months

The mean G-cell number (gastrin secretion) and the ratio of G to D cells, related somatostatin secretion, show a significant increase,

In adults, increased incidence of gastric atrophy associated with long-term use of PPIs, especially in the presence of H. pylori infection. However, similar studies are still lacking in children

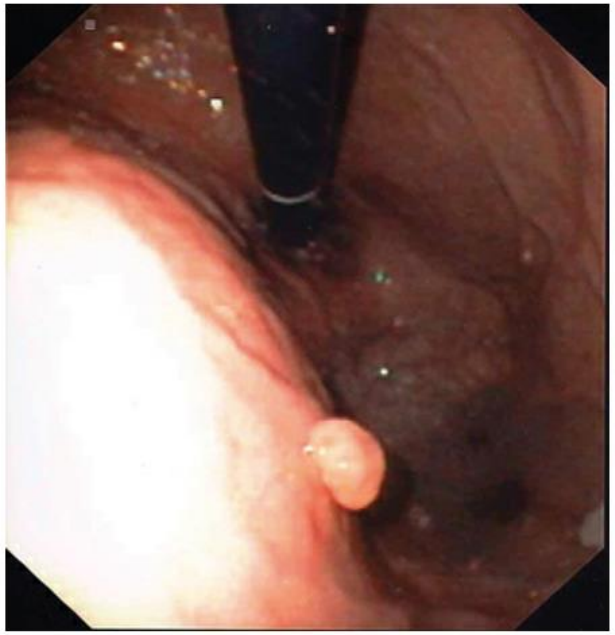
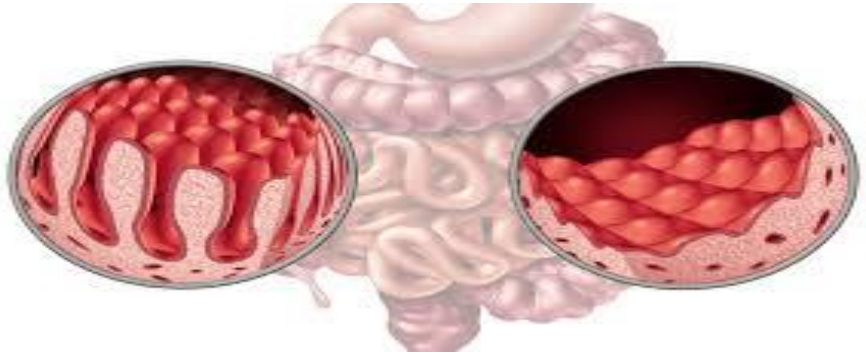


Figure 9.2-5 Multiple sessile hyperplastic polyps of the fundus in a child receiving PPI for three years.

Malabsorption



Vitamin B12

Hypomagnesemia.

Vitamin B

In children, long-term treatment with a PPI is not considered a causal factor of vitamin B12 deficiency.

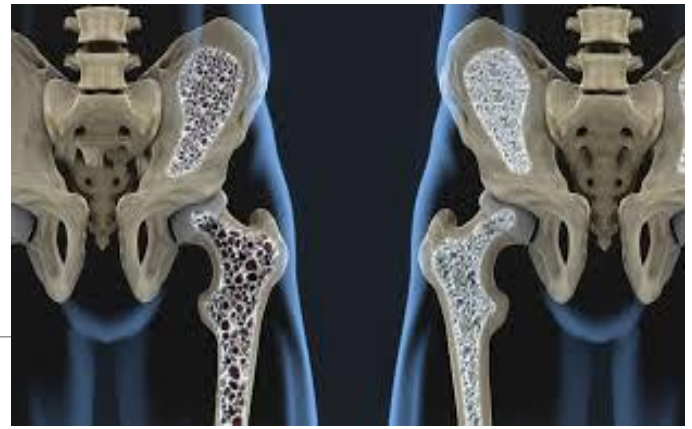
Electrolyte disturbances in children receiving omeprazole for gastroesophageal reflux disease

Table 2: Distribution of electrolyte disorders before and after omeprazole

Electrolyte disturbance	Before omeprazole, *n* (%)[e]	After omeprazole, *n* (%)[f]	*P*[g]
Sodium reduction[a]	1 (1.03)	17 (17.5)	<0.001
Calcium reduction[b]	2 (2.1)	16 (16.5)	0.001
Magnesium reduction[c]	0	10 (10.3)	0.002
Potassium reduction[d]	0	0	1

[a]Serum sodium<135 mmol/l; [b]Serum calcium <8.5 mg/dl; cSerum magnesium <1.7 mg/dl; [d]Serum potassium <3.5 mmol/l; [e]The number of patients (percent) before omeprazole consumption; [f]The number of patients (percent) after omeprazole consumption; [g]The probability of obtaining test results at least as extreme as the results observed during the test, assuming that the null hypothesis is correct

In vitro data show that osteoclast activity is inhibited by PPI (omeprazole),



In vivo studies indicate that gastric suppression by PPIs could result in decreased intestinal calcium absorption.

hyperparathyroidism and affect bone remodeling and mineralization ---------->>
bone fractures

Modest association between PPI use and an increased risk of hip and vertebral fractures

as well as affect connective tissue and muscle strength

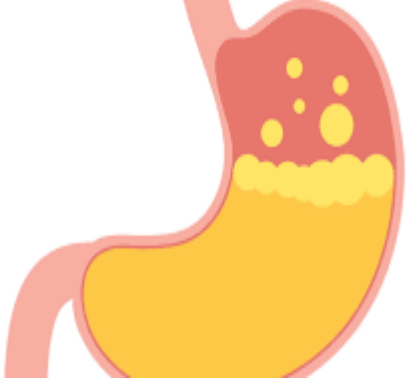
Some studies shown that omeprazole has no influence on bone turnover in children during short -term treatment. .

PPIs directly affect iron metabolism by suppressing iron absorption

1. Upregulating hepcidin, which inhibits duodenal ferroportin
2. Sideropenic anemia due to the negative effects of PPIs on iron absorption,

Vitamin B12 : Gastric acid and activated pepsin needed to release vitamin B12 from its protein bond and its subsequent binding with intrinsic factor

Prolonged rebound hypersecretion

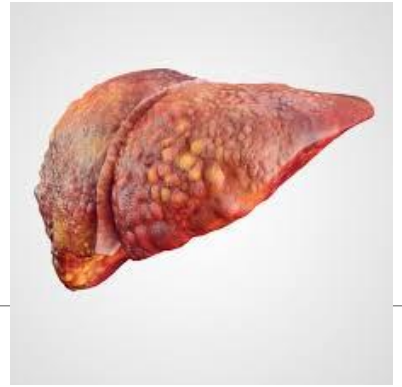


After discontinuation of a PPI ---->> increase in both basal and maximal acid output.

The phenomenon occurs after as little as two-month course of therapy and lasts for at least two months after the PPI is stopped.

Exacerbation or reoccurrence of peptic acid disease
(so tapering is need)

Omeprazole can increase the plasma concentration of diazepam, phenytoin, carbamazepine, and warfarin.



The long-term PPIs in patients with cirrhosis ----

- development of bacterial infection
- increase risk of hepatic encephalopathy

- probably due to changes in composition and metabolism of intestinal microbiota

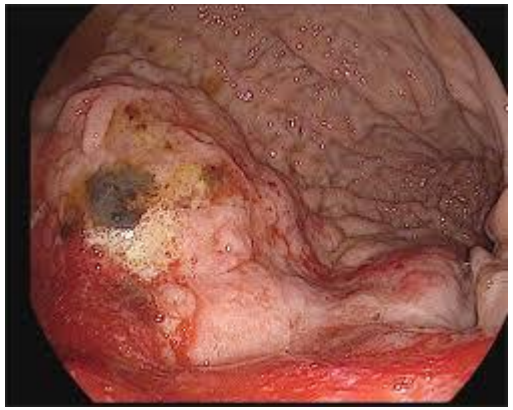
We do not know whether these findings are relevant posttransplant immunocompromised children of bacterial translocation from the gut

GASTRIN SECRETION AND GASTRIC CANCER

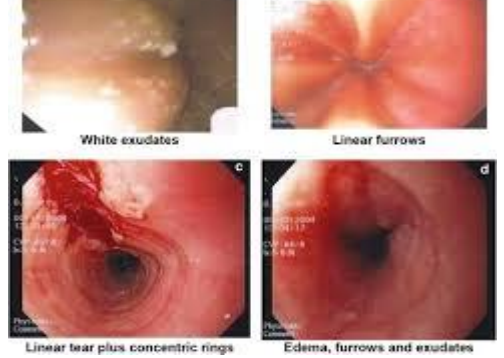
Elevated gastrin levels and enterochromaffin-like cell hyperplasia

long-term PPI use may be associated with an increased risk of gastric cancer in some studies.

- More recent studies do not support an increased risk of gastrointestinal cancers with 2 or more years of PPI use, although the risk with use >10 years needs to be better defined



SENSITIZATION TO FOOD ANTIGENS



Increase gastric pH due to therapy with PPIs prevents activation of pepsinogens and the initiation of protein digestion in the stomach

PPI therapy may lead to sensitization to food antigens

De novo EoE on long term PPIs may raise some concern.

Retrospective study showed that treatment with acid-suppressive medications, both PPIs and H 2- receptor antagonists, in the first 6 months of life, significantly increases the risk for development of food allergy, medication allergy, anaphylaxis, allergic rhinitis, and asthma.

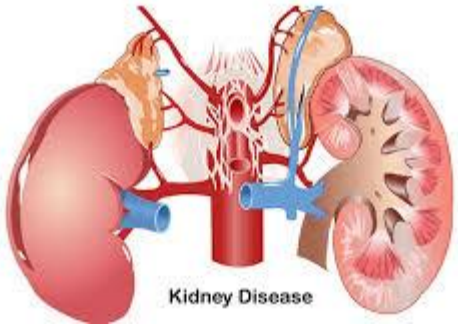
In one study exposure to antisecretory medications was associated with an increased incidence of Celiac Disease , especially in younger individuals.

Lebwohl et al addressed the possibility that symptoms of un

-diagnosed CD were the cause rather than the consequence for the

prescription of PPIs (protopathic bias);

OTHER CONDITIONS

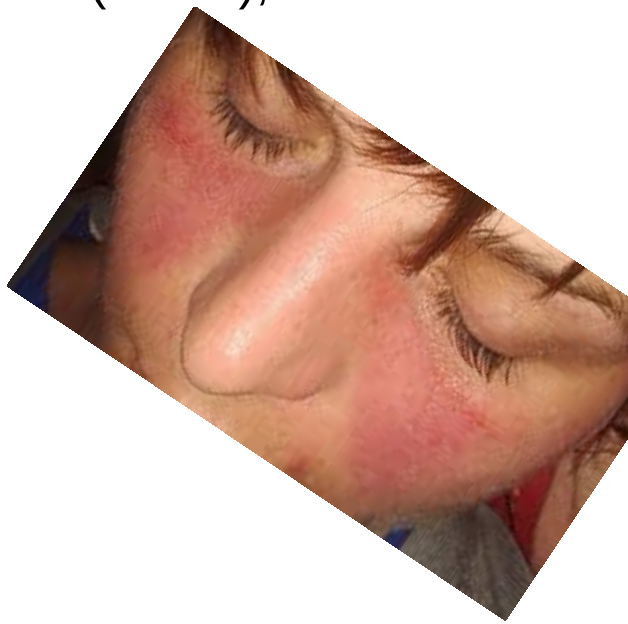


Increased risk of acute kidney injury & chronic kidney disease including end-stage renal disease in adults

Increased risk of cancers of the liver , pancreas , and colorectum

Cutaneous and systemic lupus erythematosus

Cutaneous lupus erythematosus, most often subacute cutaneous lupus erythematosus (SCLE),
reported with use of proton pump inhibitors
SCLE is reversible (resolution ~3 months following discontinuation



Mechanism: Non-dose-related; immunologic.
positive antinuclear antibodies (ANA), anti-Ro/SSA and anti-La/SSB,

~8 months following treatment initiation (range: 3 days to 3.5 years)

Systemic lupus erythematosus: According to the manufacturer, may occur within days to years after initiating treatment.