An Introduction to the Clinical Pharmacology of the Gastrointestinal Tract

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“Trust not the physician; His antidotes are poison”
William Shakespeare

* May also apply to physician assistants and nurse practitioners
Principles of Pharmacologic Therapy

• Drug prescription requires responsibility
  – Choose best treatment
  – Be aware of risks and warnings
  – Understand how to use the drug in special patient groups
    • Pregnancy, elderly, kidney and liver disease
  – Be familiar with side effects and drug interactions
  – Appropriate monitoring of patients on therapy
Principles of Pharmacotherapy: Patient Oriented Goals

- Improve symptoms of the disease
- Attenuate natural history of the disease
- Reduce or prevent disease complications
- Overall goal is to improve the patient’s quality of life
Treatment Options for GERD

- Treatment options using medications
  - Neutralize gastric acid
  - Decrease/eliminate gastric acid secretion
  - Accelerate emptying of stomach contents

- Treatment options using surgery
  - Repair hiatal hernia
  - Tighten the esophagogastric junction
GERD Treatment Options: Antacids

- TUMS, Maalox, Mylanta, Rolaids, Alka-Seltzer
- Ingredients:
  - aluminum hydroxide, calcium carbonate, magnesium hydroxide, and sodium bicarbonate
- Mechanism of action
  - Neutralization of gastric acid
- Clinical usage
  - Only effective while in the stomach
  - Useful as PRN treatment for episodic symptoms of GERD (heartburn)
  - Calcium carbonate can also function as a supplement
H2 Blockers:
cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), ranitidine (Zantac)

• How they work
  – Parietal cells have histamine, acetylcholine and gastrin receptors
  – Stimulation of these causes acid secretion
  – H2 (histamine) blockers reduce acid secretion by 50-80%
Proton pump inhibitors (PPIs)
omeprazole (Prilosec), lansoprazole (Prevacid), pantoprazole (Protonix), rabeprazole (Aciphex), esomeprazole (Nexium), dexlansoprazole (Dexilant)

• Mechanism of action
  – Acid is secreted from the parietal cell into the stomach across a large concentration gradient
  – H+/K+ ATPase, an energy-dependent proton pump, is required for this process
  – PPIs irreversibly bind to proton pump
  – These drugs inhibit >90% of total daily gastric acid production
ATP

Proton pump

Cytoplasm
pH is higher
[H+] is lower

Extracellular fluid
(in lysosomes interior)

pH is low
[H+] is higher
Omeprazole More Effective Than Ranitidine in Controlling Symptoms of Erosive Esophagitis

Omeprazole vs ranitidine (12-month Controlled Study)

- 72% Omeprazole 20 mg QD
- 45% Ranitidine 150 mg BID

% of Patients Without Symptom Relapse

Months

0 2 4 6 8 10 12

P<0.001 (Life Table Estimates)

Important drug interactions: PPIs and Clopidogrel (Plavix)

- Clopidogrel-inhibitor of ADP-induced platelet aggregation
- The CURE study 12,562 patients with acute coronary syndrome presenting within 24 hours of ischemia, EKG changes or elevated cardiac enzymes.

![Graph showing cumulative event rate](image)
Important drug interaction
PPIs and Clopidogrel (Plavix)

• Patients on clopidogrel receive PPI therapy
  – Prevent aspirin-induced ulcers
  – Decreased (50%) in GI bleeding on combination therapy*

• Omeprazole reduces antiplatelet effect of clopidogrel in half
  – More adverse cardiovascular events and increased mortality when clopidogrel combined with omeprazole**

**J Am Coll Cardiol 2008:51:256-60
PPIs and Clopidogrel (Plavix) FDA recommendations

• Consult with healthcare provider if currently taking or considering taking omeprazole with clopidogrel (including Prilosec OTC).

• Patients using clopidogrel needing medication to reduce stomach acid can use antacids and most acid reducers, such as H2 blockers.

• Tagamet and Tagamet HB (cimetidine) should not be used.
Proton pump inhibitors: Sleeping Dragons?

- Decreased vitamin B12 absorption/ possible deficiency
  - Mechanism
    - Acid is needed to liberate food-bound vitamin B12*
  - Treatment
    - Supplement crystalline vitamin B12
- Community acquired pneumonia
  - Mechanism
    - Gastric acid suppression allows upper GI bacterial overgrowth/aspiration
  - Prevention
    - Hold a few PPI doses monthly*
      * Not evidenced based recommendation
PPIs and *Clostridium difficile* Infection

• **Mechanism**
  – Gastric acid provides defense against bacterial colonization
  – *C diff* cells and spores cannot survive in acid pH
  – Hospitalized patients exposed to *C difficile* in environment
  – Possible alteration of colonic flora due to change in gastric pH
Unique Delivery Systems for GI Drugs: 5-Aminosalicylic acid (5-ASA)

• How 5-ASA works
  – Inhibits prostaglandin synthesis and production of arachidonic acid metabolites
  – Decreased inflammatory cascade
  – Free radical scavenger

• If 5-ASA taken orally, gets absorbed into the bloodstream.

• For IBD, needs to work *topically*
5-Aminosalicylic acid (5-ASA): Delivery systems to allow topical GI effect

- Bacterial cleavage of linked molecules
  - **Sulfasalazine**: 5-ASA and sulfapyridine.
  - **Olsalazine** (Dipentum): two 5-ASA molecules linked via a diazo-bond
  - **Balsalazide** (Colazal): 5-ASA molecule azo-linked to a benzoic acid derivative
5-Aminosalicylic acid (5-ASA): Delivery systems to allow topical effect

- Other delivery systems
  - **Asacol**: 5-ASA in a capsule that dissolves at pH values exceeding 7
  - **Pentasa**: 5-ASA enclosed in microspheres enclosed in an ethylcellulose semipermeable membrane.
New Delivery Systems for 5-ASA

- Aprisio
  - pH-dependent coating on tablet, delays the release of 5-ASA until pH>6 (ileum and colon)
  - Uses Intellicor™ delayed and extended delivery system
5-ASA New Delivery Systems

• Lialda
  • Uses Multi Matrix System (MMX®) Technology
    – pH-dependent coating on tablet, delays the release of 5-ASA until pH=7 (terminal ileum and colon)
    – A tablet core containing 5-ASA, swelling polymer with hydrophilic and lipophilic components

• Delivery of 5-ASA throughout the colon
• Once daily dosing
Asacol can be administered once daily

- A dynamic model of colonic concentrations of delayed-release 5-aminosalicylic acid (Asacol)

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M. P. THORPE, E. D. EHRENPREIS, K. S. PUTT, B. HANNON
Entocort: Another Unique Delivery System

- Enteric coated budesonide
- Budesonide has high first pass metabolism
- Effective treatment
  - Ileal Crohn’s disease
  - Positive data for microscopic colitis
First Pass Metabolism
Biologic Therapy for Crohn’s Disease: Delivery Systems

• Antibodies to tumor necrosis factor
  – Intravenous
    • Infliximab (Remicaide)
  – Subcutaneous
    • Adalimumab (Humira)
    • Certolizumab (Cimzia)
Administration of Biologic Therapy

• Infliximab, Natalizumab
  – Infusions are given in hospitals, surgical centers, infusion clinics, physicians offices, usually every 8 weeks

• Adalimumumab
  – Physician or other healthcare provider instructs patient prior to use. Subcutaneous injection of prefilled syringe by patient at home, every 2 weeks

• Certolizumab
  – Subcutaneous injection by physician or nurse every 4 weeks
Important serious side effects from antibiotics used for GI diseases

• Ciprofloxacin-FDA black box warning
  – Tendonitis and tendon ruptures.
  – Greatest risk
    • age >60,
    • steroid therapy
    • transplant recipients

• Metronidazole
  – Peripheral neuropathy
  – Seen with prolonged use (such as Crohn’s disease)
  – May be irreversible
Important serious side effects
Biologic therapy

• Severe infections
  – Bacterial sepsis
  – Tuberculosis
  – Invasive fungal disease
  – Other opportunistic infections
  – Lymphoma

• Patients should be checked for risk factors and tested for latent tuberculosis infection prior to therapy
Hepatosplenic T-cell lymphoma in patients receiving TNF-α inhibitor therapy: expanding the groups at risk.

- Twenty six cases of HSTCL identified
- 23 (89%) cases were in patients with IBD and 3 (11%) were in rheumatoid arthritis patients.
- 5 cases (19%) were females.
- 7 cases (27%) occurred in patients > 50 yrs of age, 4 (15%) were >65 yrs of age.
- 89% occurred in patients on a TNFα blocker plus an immunomodulator,
  - Parakkal D, Sifuentes H, Semer R, Ehrenpreis ED.
  - Eur J Gastroenterol Hepatol. 2011 Nov;23(12):1150-6
Natalizumab and Progressive Multifocal Leukoencephalopathy (PML)

- Progressive and generally fatal CNS demyelinating disease
- Usually seen in immunosuppressed patients
- Caused by reactivation of Jacob-Cruezfeld (JC) virus
- Occurred in initial drug trials
  - Two patients with multiple sclerosis
  - One patient with Crohn’s disease
Natalizumab and Progressive Multifocal Leukoencephalopathy (PML)

• Removed from the market in 2005
• Reapproved in 2008 for adults with moderately to severe Crohn’s disease unresponsive or intolerant to other treatments including inhibitors of TNF-α.
• Approved for multiple sclerosis
• Cannot be administered with other immunosuppresants
• Available via a risk management program with the manufacturers of TYSABRI and the FDA known as the TOUCH
Short term side effects of corticosteroids

- Increased intraocular pressure
- Increased blood pressure
- Increased serum glucose
- Peripheral edema
- Mood swings
- Depression
- Fatigue
- Weight gain
- Fat deposits in the face, upper back and abdomen
Long term side effects of corticosteroids

- Cataracts
- Increased risk of infections
- Osteoporosis and fractures
- Menstrual irregularities
- Adrenal gland suppression
- Capillary fragility and bruising
- Delayed wound healing
- Acne
- Depression
- Psychosis
- Myopathy
- Normal pressure hydrocephalus
- Avascular necrosis of the hip
Irritable Bowel Syndrome (IBS)
Is the treatment worse than the condition?

• Antispasmodics
  – Hyocyamine (Levsin), dicyclomine (Bentyl), atropine, scopolamine (Donnatol)
  – CNS side effects
    • Confusion, disorientation, memory loss, hallucinations, anxiety, fatigue, insomnia, psychosis, coma.
    – Can cause heat stroke from decreased sweating.
    – Dicyclomine syrup in infants
      • Apnea, seizures, syncope, coma and death.
“He's the best physician that knows the worthlessness of the most medicines.”

Benjamin Franklin