

## Treatment of Peptic Ulcer Disease (2009)

David Guay, Pharm.D.  
F.C.P.,F.C.C.P.,F.A.S.C.P

---

---

---

---

---

---

---

---

## Goals of Treatment

- Relieve pain
- Prevent complications (bleeding, perforation, penetration, obstruction)
- Minimize recurrences
- Reduce financial costs

---

---

---

---

---

---

---

---

## Medical

- Receptor antagonists (histamine, Ach, gastrin)
- Antidepressants (TCAs)
- Proton pump inhibitors (PPIs)
- Cytoprotectives (PGs)
- Coating agents (Bismuth)
- Antacids (prn)

---

---

---

---

---

---

---

---

## Histamine Blockers

Cellular Mechanisms

- H1 vs. H2 (parietal cells, uterus, heart)
- Reversible blockade
- Non-histamine receptors (androgenic, cytochrome P450, lymphocytes)

---

---

---

---

---

---

---

---

## Histamine Blockers (Cont'd)

Basic Pharmacokinetic Parameters

Drug	F (%)	T 1/2 (h)	CL (mL/min)	fe (%)
Cimetidine	60-80	2-3	600	50
Ranitidine	40-90	1.5-2	600	50
Famotidine	37-45	2.5-4	450	25-30
Nizatidine	95	1-2	750	60-65

---

---

---

---

---

---

---

---

## Oral Dosing in Patients with Normal Renal and Hepatic Function

Drug	Acute Tx	Maintenance Tx
<b>Cimetidine</b>	<ul style="list-style-type: none"> <li>■ 200 mg tid + 400 hs or 20 mg/kg/d (divided qd-qid) in children</li> <li>■ 300 mg qid</li> <li>■ 400 mg bid</li> <li>■ 800 mg hs</li> </ul>	300 or 400 mg hs or 10-15 mg/kg hs in children
<b>Ranitidine</b>	<ul style="list-style-type: none"> <li>■ 150 mg bid</li> <li>■ 300 mg hs or 6-10mg/kg/d (qd or bid) in children</li> </ul>	
<b>Famotidine</b>	40 mg hs	20 mg hs
<b>Nizatidine</b>	<ul style="list-style-type: none"> <li>■ 150 mg bid</li> <li>■ 300 mg hs</li> </ul>	150 mg hs

---

---

---

---

---

---

---

---

## Dosing in Renal Failure (mg/d)

Drug	Normal	Cr Cl 130-75	Cr Cl 30-15	Cr Cl 5-15	Cr Cl <5
Cimetidine	800	800	600	400	200-400
Ranitidine	300	150-300	150	75-150	75-150
Famotidine	40	20-40	10-20	10-20	10
Nizatidine	300	150	150	150 Q48h	150 Q48H

---

---

---

---

---

---

---

---

## Clinical Use

- **Smokers vs. nonsmokers in acute and maintenance treatment**
- Effects of smoking on PUD
  - Increased rate of gastric emptying
  - Diminished pancreatic bicarbonate secretion
  - Decreased duodenal pH
  - Reduced mucosal blood flow
  - Inhibition of mucosal prostaglandins
- Duration of Acute Tx
  - Uncomplicated DU = 4 + wks
  - Uncomplicated GU = 6 + wks

---

---

---

---

---

---

---

---

## Clinical Use (cont'd)

- NSAIDs**
- Std. doses heal DU even when NSAID cont'd but no effect on GU (DU needs double-dose therapy for longer time)
  - Std. doses prevent NSAID-assoc. DU but not GU
  - Double-dose therapy prevents NSAID-assoc. DU + GU-? role vs. PPI/misoprostol (effect inconsistent)
  - ZES-Obsolete (use IV and PO PPI)

---

---

---

---

---

---

---

---

## Side Effects

- 4-5% overall
- Approximately same for all
- CNS: sedation, depression, agitation, confusion
  - Patients at risk = elderly, hepatic or renal dysfunction ? cimetidine the worst
  - Penetration into CNS in liver disease is ↑
- Hematologic-dec. platelets, WBC, all lines-rare!
- Hepatitis-rare!
- Endocrine: androgen receptors (galactorrhea, gynecomastia, impotence) even in std. doses
- Safe in pregnancy (ranitidine DOC)
- ↓ AEs by adj. dose for renal fx

---

---

---

---

---

---

---

---

## Drug-Drug Interactions

- Hepatic blood flow vs. cytochrome P450 enzyme inhibition vs. inhibition of renal tubular secretion vs. inhibition of drug absorption
- No interaction with ethanol (alcohol dehydrogenase)

---

---

---

---

---

---

---

---

## Proton Pump Inhibitors (PPI) (Omeprazole As Prototype)

Cellular mechanisms

- H<sub>2</sub>K-ATPase-tissue-specific (only parietal cell)
- All forms of stimulated acid secretion are blocked
- Omeprazole is inactive prodrug at pH = 7 but activated at pH < 3 (canaliculus)
- Can produce total anacidity
- Effects on gastrin

---

---

---

---

---

---

---

---

## Omeprazole (cont'd)

### Pharmacokinetics

- F approx. 50% (buffered solution), 65% (EC)
- Absorbed best on empty stomach (acid labile)
- Bioavailability increased over first five days of therapy
- Extensively metabolized-hydroxy, sulfone, sulfide
- $t_{1/2} = 0.5-1.5$  hr
- No correlation of plasma conc. with acid secretory inhibition (accumulates in parietal cell)

---

---

---

---

---

---

---

---

## Omeprazole (cont'd)

- Dosing in patients with normal renal and hepatic function, ↓ renal function
  - 20mg or 40mg once daily in a.m.
  - Peds-0.6mg/kg/d (grans from emptied capsules on sauce/yogurt, juice, omeprazole-sod. bicarb prep.)

---

---

---

---

---

---

---

---

## Clinical Use

- Faster symptom relief and healing than H2RAs
- Efficacy vs. H2RA-resistant ulcers and ZES (DOC, greater than 80 mg/d, use bid dosing)
- Equal to misoprostol and superior to H2RAs in healing NSAID-assoc. ulcers, esp. if NSAID to be continued
- Prevents NSAID DU+GU (in most cases, DOC as tolerated better than misoprostol)
- No rationale for combined omeprazole-H2RA use
- ? Safety in maintenance therapy

---

---

---

---

---

---

---

---

## Side Effects

- ? Hypergastrinemia → enterochromaffin-like cell hyperplasia → gastric carcinoma in rats (early 80's)
- Bacterial overgrowth in stomach → incr. nitrates/nitrosamines → carcinoma
- Above → reluctance to examine maintenance tx
- PPI acute tx → H2RA maintenance tx
- Pregnancy-safe

---

---

---

---

---

---

---

---

## Drug-Drug Interactions

- CYP 450 enzyme inhibitor, esp. if dose greater than 40mg/d (GERD, ZES) e.g. diazepam, antipyrine, phenytoin
- ? Sulfone metabolite the instigator
- Omeprazole has greater potential to inhibit enzymes vs. other PPIs
- Pancreatic enzyme tx-omeprazole may decrease inactivation
- ? Omeprazole effect on ketoconazole, tetracycline absorption (pH)
- May increase BA of bismuth

---

---

---

---

---

---

---

---

## Other Proton Pump Inhibitors

- Dexlansoprazole (Kapidex)
- Lansoprazole (Prevacid)
- Rabeprazole (Aciphex)
- Pantoprazole (Protonix)
- Esomeprazole (Nexium)
- Dose equivalency:  
omep 20mg = esomep 20mg = rabep 20mg =  
panto 40mg = lanso 30 mg (dexlans – unclear)

---

---

---

---

---

---

---

---

## Choice of PPIs

- Can open osage form and sprinkle on food, etc. to admin.: omep, lanso, dexlanso, esomep
- Can open dosage form and admin. as susp., including down feeding tubes: omep, lanso, esomep, panto
- No alternative dosing avail.: rabep
- IV dosing: esomep, lanso, panto

---

---

---

---

---

---

---

---

## Prostaglandins

- Analogues: misoprostol, enprostil, arbaprostil, trimoprostil, rioprostil
- Work via acid secretion inhibition (major mech.) and perhaps "cytoprotection"

---

---

---

---

---

---

---

---

## Clinical Use

- Duodenal and gastric acute ulcer healing – works but 1<sup>st</sup> line tx
- Decreases GI mucosal irritation and blood loss due to NSAIDs, prevents GU and DU due to NSAIDs, reduces NSAID DU/GU complication rates, heals NSAID GU and DU even during cont'd NSAID tx (need minimum of 400 mcg/day)
- Maintenance tx – no data for non-NSAID DU/GU

---

---

---

---

---

---

---

---

## Clinical Use (cont'd)

- Target patient:
  1. history of DU/GU, regardless of relationship to NSAID, with /without complications, when NSAIDs must be used,
  2. very elderly and high surgical risk if ulcer complications occurred,
  3. NSAID + corticosteroids,
  4. NSAID + anticoagulants,
  5. 2 + NSAIDs,
  6. NSAID + bisphosphonate

---

---

---

---

---

---

---

---

## Approach to NSAID PUD Prevention When An NSAID is Needed

<u>Risk Level</u>	<u>Recommendation</u>
Low (zero RFs)	Use safest traditional NSAID (minimum ther. dose)
Moderate (1-2 RFs)	Use combo of safest traditional NSAID or celecoxib plus either PPI or misoprostol or double-dose H2RA

---

---

---

---

---

---

---

---

## Approach to NSAID PUD Prevention When An NSAID is Needed (cont'd)

<u>Risk Level</u>	<u>Recommendation</u>
High ( $\geq 3$ RFs or on ASA or warfarin or steroids)	Celecoxib + PPI or miso (on ASA) Celecoxib + miso (on warfarin) Celecoxib (on steroids)
Very High (history of Prior PUD complications)	Avoid all NSAIDs or use celecoxib + miso or PPI

---

---

---

---

---

---

---

---

## Side Effects

- Diarrhea-30-40% loosening, 5% frank diarrhea
- Abdominal pain (cramps)
- Uterine bleeding/spontaneous abortion (category X)
- Avoid in nursing mothers (infantile diarrhea)

---

---

---

---

---

---

---

---

## Sucralfate

### Chemistry and Mechanism of Action:

- Acid → adheres to defective mucosa → barrier
- Weak acid neutralizer, inhibits pepsin, binds bile salts, stimulates mucus production
- ? "cytoprotective" via stimulation of PG synthesis/release

### Pharmacokinetics:

- "Nonabsorbed" – beware AI in ESRD

---

---

---

---

---

---

---

---

## Sucralfate (cont'd)

### Dosage:

- 1 g qid (1 hr ac+hs) – tx of DU/GU
- 2 g bid (1 hr ac) – tx of DU/GU
- 1 g bid (1 hr ac) – maint. tx of DU (? 2 g hs)
- 1 g am ac + 2 g hs – maint. tx of GU

### Clinical Use:

- Don't use for maintenance tx as need to give bid
- Don't use for NSAID PUD tx/prevention

---

---

---

---

---

---

---

---

## Sucralfate (cont'd)

### Side Effects:

- < 5% of patients
- GI
- Constipation most significant
- Hypophosphatemia (osteomalacia)
- DOC in pregnancy

### Drug Interactions:

- Adsorption (chelation) – phenytoin, warfarin, fluoroquinolones, thyroxine

---

---

---

---

---

---

---

---

## Antacids

- $\text{NaHCO}_3$
- $\text{CaCO}_3$
- $\text{Al(OH)}_3$
- $\text{Mg(OH)}_2$

---

---

---

---

---

---

---

---

## Chemistry and Mechanism of Action

- Neutralize gastric acid
- Decrease postprandial acid secretion
- Adsorbs pepsin ( $\text{Al(OH)}_3$ )
- Adsorbs bile acids
- "Cytoprotective"

---

---

---

---

---

---

---

---

## Pharmacokinetics

- Absorbable:  $\text{NaHCO}_3$  (F = 100%),  $\text{CaCO}_3$  (F = 25-30%)
- "Nonabsorbable":  $\text{Al}(\text{OH})_3$ ,  $\text{Mg}(\text{OH})_2$

---

---

---

---

---

---

---

---

## Side Effects

- Hypercalcemia, hypermagnesemia
- Constipation – Al, Ca
- Diarrhea – Mg
- Flatulence –  $\text{NaHCO}_3$
- Aluminum intoxication – CRI, ESRD
- Sodium load
- Safe in pregnancy

---

---

---

---

---

---

---

---

## Drug-Drug Interactions

- Chelation of tetracyclines, iron, calcium, quinolones
- ↓ absorption of drugs requiring acid pH (e.g. tetracyclines, ketoconazole)

---

---

---

---

---

---

---

---

### *Helicobacter pylori* Antibiotherapy

1. All *H. pylori* infected patients with PUD should be tx (initial presentation or recurrence)
2. All infected PUD patients on maint. tx or with a hx of complicated or refractory dz should be tx
3. Infection must be demonstrated first (serology is easiest way)
4. No tx GERD, even if infected
5. Role of HP in NSAID PUD controversial although meta-analysis suggests a role (see later)

---

---

---

---

---

---

---

---

### HP Antibiotherapy (cont'd)

1. PPI + Amox 1 g BID + Clari 500 mg BID, all x 14 days ("OAC")
2. PPI + Metro 500 mg BID + Clari 500 mg BID, all x 14 days ("MOC")
3. Bi 525 mg QID + Metro 250 mg QID + Tetra 500 mg QID + either PPI or ranit 150 mg BID, all x 10-14 days (augmented "Std. Triple Therapy")
4. PPI + Amox 1 g BID, both x 5 days → PPI + Clari 500 mg BID + Tinidazole 500 mg BID, all x 5 days

---

---

---

---

---

---

---

---

### HP Antibiotherapy (cont'd)

- Double-dose PPI = double-dose H2RA as components of HP eradication tx (omep. 20 mg bid = ranitidine 300 mg bid)
- All PPI's equivalent in HP eradication tx (omep 20 mg bid = lanso 30 mg bid = rabep 20 mg bid = esomep 20 mg bid or 40 mg qd = pantop 40 mg bid) – no data with dexlansoprazole
- Std. PPI/H2RA dose qd is inferior to same dose bid in HP erad. (esomep may be exception)
- Further ↑ in PPI dose or ↑ duration of tx does not ↑ erad. rates

---

---

---

---

---

---

---

---

## HP Antibiotherapy (cont'd)

- Decreased recurrences of DU, GU and increased healing of recurrent DU
- Decreased bleeding recurrences in bleeding PUD (still keep patient on maintenance antisecretory drug although duration is unclear)
- Controversy re "testing for cure" – fecal antigen test after 2 weeks off tx

---

---

---

---

---

---

---

---

## HP Antibiotherapy (cont'd)

- Problems: resistance (in US. clari = 12%, metro = 30%), ADR, relapse/reinfection rates, approach to renal failure pts. (Bi, tetra, dose-adjust? OAC in std. doses X 7 d works and is safe), pregnancy (delay tx until post-delivery)
- NSAID PUD
  - HP erad. prevents NSAID PUD (both GU + DU)
  - if ulcer hx and HP+, erad. HP before beginning NSAID
  - if HP+, erad. if want to use PPI NSAID proph. (HP + reduces PPI efficacy)
  - HP erad. alone is NOT sufficient as NSAID PUD proph. (still need gastroprotectant)

---

---

---

---

---

---

---

---

## HP Antibiotherapy (cont'd)

### Failure of First-Line Therapy

- if non-bismuth-based tx failed, give PPI + BMT/BMA (↑ metro to 1.5 or 2 g/d)
- use same regimen as previously but substitute metro for clari and vice versa
- if fails again, scope and get material for culture + sensitivity

---

---

---

---

---

---

---

---

### Treatment Options for the Eradication of *Helicobacter Pylori* in Children

- Same regimens as adults, adj. to body wt
- Resistance bigger issue
- 2nd line options are PPI + BMA/BMC/BMT (latter, if old enough)

---

---

---

---

---

---

---

---

### Idiopathic Ulcer Disease Treatment

- R/O *H. pylori* and NSAID use
- Biopsy GU + DU (cancer)
- < 5% of PUD
- PPI therapy (may need higher than usual PUD doses due to resistance to acid suppression)

---

---

---

---

---

---

---

---

### UGI Bleeding

- most dangerous ulcer complication
- primary treatment is endoscopy with procedure to arrest bleeding (heater probe, laser, epinephrine/sclerosant/thrombin/fibrin/glue, combinations of these, etc.)
- post-endoscopy PPI for ulcer tx (need pH  $\geq$  6 to prevent rebleed) – start with IV (80 mg bolus  $\rightarrow$  8 mg/hr x 72 hr) then  $\rightarrow$  PO if high-risk endoscopic signs
- can use PO PPI throughout if has low-risk endoscopic signs
- post-hospital oral PPI to prevent rebleed even if you can eliminate the precipitant(s) – duration is not resolved yet
- erad. HP

---

---

---

---

---

---

---

---