Prokinetics in SIBO & Motility Disorders

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Prokinetics: Definition

• Increase transit/motility in GI tract
• Improve coordination of GI movement
  – Increase LES tone, relax pylorus
  – Amplify & coordinate GI muscular contractions
• Can have different sites of action: upper or lower GI
• Vs Laxative = stimulate BM’s, loosen stool
  – Pk can be laxative but often aren’t, esp at low dose
  – Pk can be used w/diarrhea to (+) upper GI motility, esp at lower dose

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Key Points

Not all prokinetics are unsafe

Side Effects/Reactions are common
Prucalopride helps:
- nausea, bloating, pain, constipation
- (Emmanuel et al.'15)

Iberogast helps:
- nausea, GERD, bloating, cramping/pain, constipation, diarrhea
- (Ottillinger et al.'13)

Adapted from Scarpignato '98 and '12, with Ottillinger '13

<table>
<thead>
<tr>
<th>Compound</th>
<th>Crossing ER barrier</th>
<th>Antimotility effect</th>
<th>Activity on proximal gut</th>
<th>Activity on distal gut</th>
<th>Unwanted effects</th>
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<td>no</td>
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</table>

Prokinetics: Mechanisms of Action
- Muscarinic Acetylcholine Receptor Agonist: M (+)
- Acetylcholinesterase Inhibitor: ACh (-)
- Dopamine, Receptor Antagonist: D2(-)
- Serotonin, Receptor Antagonist: 5-HT3 (-)
- Serotonin, Receptor Agonist: 5-HT4 (+) = (+) ACh
- Motilin Receptor Agonist
- Cholecystokinin A Receptor Antagonist: CCK-A (-)
- Opioid Receptor Antagonist

Adapted from Scarpignato '98 with Manabe '10, Simmen '06

<table>
<thead>
<tr>
<th>Compound</th>
<th>5-HT2 receptor agonist</th>
<th>5-HT1 receptor antagonist</th>
<th>5-HT3 receptor antagonist</th>
<th>5-HT4 receptor agonist</th>
<th>M3 receptor antagonist</th>
<th>Opioid receptor antagonist</th>
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</tbody>
</table>
Prokinetic Usage

1. Symptom Relief in Motility or Functional GI Disorders
   - Dosed: tid before meals. Or after/in between meals and first a.m.
   - for GERD, dyspepsia/gastroparesis (sx after meals), bloating
   - Dosed: qd may enough for constipation depending on Pk
   - Dose: standard Pk dose

2. Prevention of SIBO Relapse (maintenance of remission)
   - Dosed: before bed
   - to (+) MMC overnight
   - Dose: low dose

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Prokinetics Usage

1. Symptom Relief
   - TID (or QD constipation)
   - Regular dose

2. SIBO Relapse Prevention
   - HS
   - Low Dose

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Prokinetic Dose

Motility, FGI Disorders Sx Relief

- Pharmaceutical
  - Low Dose Erythromycin (LDE) 50-100 mg tid-qid
  - Prucalopride 1-4mg qd or 3mg bid-tid
  - Low Dose Naltrexone (LDN) 2.5-4.5 mg hs or bid
  - 5-mg- diarrhea, 4.5-mg- constipation

- Herbal
  - Iberogast 20 drops tid or PRN
  - Ginger 500mg tid, 1000mg bid
  - MP 2-3caps bid-tid (5HTp, Acetyl L Carnitine, Ginger, Vit C, B6)

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### Prokinetic Dose

**SIBO Relapse Prevention**

- **Pharmaceutical**
  - Low Dose Erythromycin (LDE) 50-62.5 mg at bedtime (hs)
  - Low Dose Prucalopride (LDP) 0.5 mg hs (up to 2 mg if needed)
  - Low Dose Naltrexone (LDN) 2.5-4.5 mg hs or bid
  - 2-mg: diarrhea, 4-mg: constipation

- **Herbal**
  - Iberogast 30-60 drops hs
  - Ginger 1000mg hs
  - MP 2-3 caps hs or hs & a.m. (5HTP, Acetyl L Carnitine, Ginger, Vit C, B6)

### Erythromycin & Prucalopride

- **LDE**
  - No/weak Abx activity at low dose. Standard Tx for Gastroparesis
  - Delayed SIBO relapse by 3.5 mo (Pimentel '09)

- **Prucalopride**
  - Safer stronger alternative to Tegaserod which delayed SIBO relapse by 6mo (Pimentel '09)
  - Dr P thinks may help heal MMC over time. 1's choice of many GE most effective Pl
  - SE: h/a, urinary urge, temporary diarrhea, varied. Tolerance possible.

### LDN & Iberogast

- **LDN**
  - 68% success for SIBO Prevention, 38% failure (Ploesser '10)
  - Doesn’t work as Pl (not strong enough) in many (Combine w/other Pl)
  - SE: varied, sleep disturbance - titrate up to help avoid
  - Also used for inflammation, depression, Auto Immune dz (=PI-IBS)

- **Iberogast**
  - 75-85% success= IBS. Significant Sx improvement= Dyspepsia
  - Miracle for nausea
  - More effective vs metoclopramide, similar vs cisapride = Dyspepsia
  - SE: 0.04%. Safe for long term use, pregnancy, children
Ginger & MP

- Ginger
  - MoA: + gastric emptying/MMC, M Rec (+), 5-HT3 (-)
    (Micklefield '99, Hsu '99, Haniadka '13, Wu '08, Thompson '04)
  - SE: 28% GERD/Ginger Burn (Thompson '04)
    - helped by drinking water

- MP (no studies)
  - Ginger, 5HTP, acetyl L-carnitine, Vit C, B6
    - MoA: + extra ACh/Cholinergic
  - SE: GERD, diarrhea (+ LI motility too)

Japanese Daikenchuto

- Motilin agonist + lots more (Terahata '99, Negoro '99, Mochnick '01)
  - Thought to affect distal SI & LI motility (Saiki '05)
  - 90mg/kg/day (Endo '14) or 5g tid before meals
  - Processed Ginger 5-9g + Ginseng 3g + Sichuan Pepper (Zanthoxylum piperitum) 2g

Bitter Orange (immature/fructus auranti /Zhi Shi/poncirus fructus)

- 5-HT4 (+) (Qiu '11, Jiang '14, Shim '10)
  - ingredient in Chaihu Shugan San

Triphala

- mild prokinetic, laxative (Mukherjee '97, Tamhane '97)

Other Natural Prokinetics

How To Choose Pk

- When you need to be sure: choose Pruc or LDE
  - Pruc: need effectiveness, chronic cases, constipation, PI-IBS
  - LDE: chronic/recurrent cases w/o constipation, gastroparesis
  - LDN: inflammation, auto-immunity, depression
  - Iberogast: want natural, broad sx relief, nausea
  - Ginger: nausea/gastroparesis, not w/GERD
  - MP: constipation, depression, not w/GERD

- PARQ patient & ask their input
Pk PARQ: Pro’s & Con’s

- **Prucalopride**: Pro: strongest, safe (no QT/p450), low se, may heal MMC over time. Con: possible, expensive, p<30 to get in mail/not FDA approved
- **Eryth**: Pro: studied for SIBO, inexpensive/easily available, low se. Con: tolerance/se possible, long term low dose Abs, p<30 interactions. Cx: preexist HT cond (can prolong QT); w/ Berb (p450)
- **LDN**: Pro: anti-inflam, used for AI dz & depression, natural MoA. Con: not strong enough for some (1/3+); tech not Pk; se: sleep disturbance
- **Iberogast**: Pro: natural, well studied as a Pk, broad GI sx relief, safe; kids, preg, sitosterol, no s.e.’s in studies. Con: not strong enough for many, indiv se poss
- **Ginger**: Pro: natural, anti-nausea/inflam. Con: se: GERD/ginger burn, tolerance, not strong enough for many
- **MP**: Pro: (+) BM’s/LI motility, anti-depressant/sleep aid. Con: (+) BM’s/LI motility, (+) GERD/ginger burn, emotional, se: not strong enough for many

Start/Duration/Stop

- **Start**: Sx Relief- any time
  - Dr. Scarp suggests LI purging n to avoid anti-peristalsis (not w/diarrhea pt)
- **Start**: SIBO prevention- 1-5 days after tx
  - Important to be on Pk between tx courses to hold gains/prevent relapse
    - Plan ahead: Give the Rx/Pk when Tx is given
- **Duration**: Sx: ongoing PRN. SIBO: min 3mo, ongoing for many
  - May be stopped at any time- only risk is relapse of Sx or SIBO
- **Stop**: Titrate down slowly, esp w/SIBO to catch a relapse

Other Motility Considerations

- **Stress**
  - Decrease stress/sympathetic: Rushing, worrying
  - Increase parasympathetic: Conscious breaths, Gratitude, Rest
- **Meal Spacing/ Overnight Fast**
  - 4-5 hrs between meals, 12 hr overnight fast to optimize MMC
- **Physical Tx/Body work**
  - Wurn technique, visceral manipulation, cranial osteopathy ...
Pk: Pregnancy, Lactation & Pediatrics

- Preg & Lact:
  - There are no category listing for the low Rx Pk doses used
  - LDE (Cat B at regular Abs dose)
  - Prucalopride is analogous to US Cat B (at regular 2-4mg dose)
  - Safe: LDN, Iberogast, Ginger (max 2g/d)

- Peds Doses: LDE 0.25mg, LDN & Prucalopride 0.001mg/kg, Iberogast 10-30 gtt, Ginger 250mg