

Irritable Bowel Syndrome: Last year FODMAPs, this year bile acids

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Disclosures

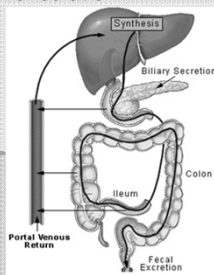
- I have no financial conflicts of interest relevant to this talk
- I will be discussing off-label indications for pharmaceutical agents

Objectives

- After this session the learner will be able to:
 - Recognize the role of bile acid malabsorption in patients with chronic diarrhea
 - Describe diagnostic tests for bile acid malabsorption and determine whether these are clinically relevant
 - List potential therapies for bile acid malabsorption

Bile physiology

- **Enterohepatic circulation**
- **Primary bile acids**
 - Cholic acid, chenodeoxycholic acid
 - Conjugated in liver
- **Secondary bile acids**
 - Deoxycholic acid, lithocholic acid
 - Modified by bacteria
 - Increases passive colonic absorption



Barkun et al. *Can J Gastro* 2013;27:653-659

Bile Acids and Diarrhea

- Increased bile acids in the colon → salt and water secretion → choleric diarrhea
- Ileal resection <100 cm
 - Negative feedback disrupted
 - Increased bile acid synthesis
 - Increased unabsorbed bile acids reach colon
- Ileal resection >100 cm
 - Reduced absorption exceeds liver's ability to synthesize bile acids
 - Fat malabsorption


Surawicz *Curr Gastro Rep* 2010

Bile Acid Malabsorption

- **Type 1**
 - Due to ileal dysfunction (Crohn's, resection)
- **Type 2**
 - "Idiopathic"
- **Type 3**
 - Due to GI disorders without ileal dysfunction
 - Cholecystectomy, vagotomy, bacterial overgrowth, celiac, microscopic colitis

Barkun et al. *Can J Gastro* 2013;27:653-659

Investigations



- SeHCAT test
 - Sensitivity >80%, specificity >98%
 - Radiolabelled synthetic bile acid ingested orally
 - Gamma camera to detect residual radioactivity at day 7
 - <10% retained at day 7 is gold standard for BAM
 - Not routinely available, not approved in US
 - Research tool mainly
- Serum C4 level
 - Intermediate in primary bile acid synthesis
 - Increased in bile acid malabsorption
 - Research tool
- Fecal bile acids
 - Available, difficult to interpret, unpleasant for patient

Prevalence

- Systematic review 15 studies of patients with diarrhea predominant IBS (n=1223)
- Based on SeHCAT testing (<10% retention)
- Prevalence of BAM 32%
- This extrapolates to 1% of the population
- Under diagnosed?
 - Survey of British Gastroenterologists
 - 61% never or rarely consider the diagnosis
 - Only 1/3 use a formal diagnostic test

Wedlake et al *Aliment Pharmacol Ther* 2009 Khalid et al *Clinical Medicine* 2010

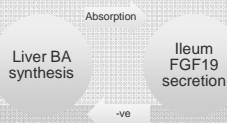
Mechanism

- Rare mutations in ileal bile transporters
 - Not identified in IBS patients with BAM
- No difference in ileal bile acid uptake
- Increase in enterohepatic cycling?
 - Each additional cycle will result in additional 5% loss of bile acid pool
- Enlarged bile acid pool seen in patients with idiopathic BAM
 - Depleted pool in patients with ileal resection
 - Overwhelms ileal absorption

Balesaria *Eur J Gastro Hep* 2008 Van Tilburg *Scand J Gastro* 1992

Disordered negative feedback

- IBS patients with +ve SeHCAT test
- High levels of C4 (serum bile acid)
- Low levels of Fibroblast Growth Factor 19
- Impaired feedback → increased bile acid synthesis → exceeds ileal absorption → diarrhea



Walters Clin Gastro Hep 2009

Bile acids and Bacteria

- Altered microbiome in IBS
- Bacterial role in deconjugating and transforming primary bile acids into secondary bile acids
- Higher levels of primary bile acids in stool of IBS patients vs controls
 - Correlated with stool frequency, consistency
- Reduced bifidobacteria, increased E coli in IBS patients
- Bile acids cause visceral hypersensitivity in human models
- Causative link not established

Duboc et al Neurogastroent and Motility 2012 Bampton Am J Physiol 2002

Investigations

- Therapeutic trial of bile acid sequestrant
 - Bind to organic ions such as bile acids
- Supported by AGA and BSG practice guidelines for chronic diarrhea
- “this approach has not been prospectively studied”

Gastroenterology 1999;116:1461-3 Thomas et al Gut 2003;52:v1-5

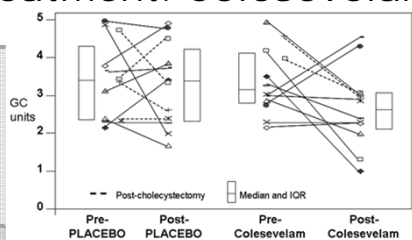
Treatment: Colestipol

- Off label use
- Bile acid sequestrant (Colestid)
- No clinical trials in bile acid malabsorption
- Lipid dosing = 2g-16g daily
- Granules (5 gram) or tablets (1 gram)
- Adverse effects
 - Constipation, abdo pain, bloating, heartburn, nausea

Treatment: Colesevelam

- Off label use
- Bile acid sequestrant (Welchol, Lodalys)
 - Water insoluble polymer
- No good quality studies
- Lipid dosing: 6X625 mg tabs/day or 3.75 gram packet/day
- Adverse effects: constipation, nausea, dyspepsia

Treatment: Colesevelam



- N=12 each arm
- Colesevelam 1.875 g bid vs placebo
- Slowed colon transit (p=0.22)

Odunsi,Shivanbade et al Clin Gastro Hep 2010

Bile Acid Sequestrant FYI

- Drug interactions
 - Oral hypoglycemics, antibiotics, warfarin, levothyroxine, olmesartan, digoxin, cyclosporin, oral contraceptives
 - Give other meds 1 hour prior or 4-6 hours after bile salt binder
 - Consult pharmacist
- Fat soluble vitamin malabsorption
 - Monitor vitamin A, E, INR periodically if long term use

Barkun et al *Can J Gastro* 2013;27:653-659

Diet therapy?

- Low fat diet
 - Recommended in ileal resection
 - In IBS bile acid pool is enlarged, so should not make a difference
- Sun dried raisins
 - Lower total fecal bile acid concentrations
- Jacquez wine (Madeira)
 - Non-specific diarrheal properties
 - Inhibits bile acid diarrhea in mice

Spiller *J Med Food* 2003 Vitali *Phytother Res*

Post-cholecystectomy diarrhea

- 10-20% prevalence
- Loss of reservoir function of gall bladder
- Increased delivery and cycling of bile acids to terminal ileum
- Case series evidence only
 - Cholestyramine (2-12 g/day) normalized BM's in 92%
 - When discontinued, 61% maintained regular BMs
 - Mean 3.9 yrs of treatment

Sciaretta *Am J Gastro* 1992

Conclusions

- Bile acid malabsorption is a common cause of chronic diarrhea
- Empirical trial of a bile acid sequestering agent is effective to
 - Rule out the diagnosis
 - Treat the patient

Questions?

Snapshots at jasonlove.com



"I'm afraid that your irritable bowel syndrome has progressed. You now have furious and vindictive bowel syndrome."
