Constipation & Defecation Disorders

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DEFINITION

• What physicians mean:
  – Less frequent bowel movements
  – Abnormal stool form
  – Smaller bowel movements
  – (Dyschezia)

• What patients mean:
  – “I haven’t had a bowel movement today.”
  – “My stools are hard and lumpy.”
  – “It’s hard to have a bowel movement.”
CONSTIPATION SYMPTOM COMPLEX

WHAT’S NORMAL?

• Stool frequency
  – In most surveys 3 BM/week to 2 BM/day
  – Depends in part on diet\(^1\)
    • Healthy young men had $25.2 \pm 1.4$ BM/month
    • Dropped to $19.0 \pm 2.3$ BM/month on low fiber diet
    • Increased to $40.3 \pm 4.9$ BM/month on high fiber diet

• Stool consistency ("hardness")
  – Small range when measured objectively\(^2\)
  – Did not differ significantly between normal subjects and constipated patients

\(^1\)Tucker et al. *Gastroenterology* 1981;81:879-83
STOOL CHARACTERISTICS

• Normal individuals (N=20)
  – Frequency
    • 7.1 + 0.3 BM/week
    • ~1 BM/day
  – Weight
    • 589.4 + 60.2 g/week
    • 84.5 + 8.1 g/BM
  – % solids
    • 29.0 + 0.8%
  – Physical hardness
    • 26.6 + 3.9 g

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• Constipated individuals (N=20)
  – Frequency
    • 1.7 + 0.2 BM/week*
    • ~0.24 BM/day
  – Weight
    • 153.4 + 27.0 g/week*
    • 90.3 + 12.3 g/BM
  – % solids
    • 31.7 + 0.8%
  – Physical hardness
    • 39.3 + 7.0 g

*P<0.001 vs. normals

BRISTOL STOOL FORM

- Seven categories defined
- Form depends upon colon transit time
  - Lumpier stools correlate with longer colon transit
- Often used in studies
- Subjective
- Categorical variable
  - Should not average results

1Davies et al. Gut 1986;27:164-169
DEFINITIONAL PROBLEMS WITH STUDIES

• Constipation not always defined precisely
  – Criteria not employed or specified
  – Many coexisting symptoms

• Symptom of constipation not always fully evaluated
  – May be secondary to some disease process
  – Confusion between symptom and condition of idiopathic or functional constipation

• Confusion between “irritable bowel syndrome with constipation” and “functional constipation”
ROME III CRITERIA FOR FUNCTIONAL CONSTIPATION¹

• At least 3 months in the preceding 6 months of two or more of:
  – Straining in >1/4 defecations
  – Lumpy or hard stools in >1/4 defecations
  – Sensation of incomplete evacuation in >1/4 defecations
  – Sensation of anorectal obstruction/blockade in >1/4 defecations
  – Manual maneuvers to facilitate >1/4 defecations (e.g., digital evacuation, support of the pelvic floor); and/or
  – <3 defecations/week

• Loose stools not present. Insufficient criteria for IBS.

CONSTIPATION AS A SYMPTOM

• Constipation may be due to other diseases/conditions
  – Mechanical obstruction
  – Metabolic diseases
  – Painful anorectal conditions
  – Collagen-vascular disease
  – Neurological diseases
  – Pregnancy
  – Medications

• Constipation may be idiopathic
  – Slow transit constipation
  – Functional outlet obstruction
NORMAL FUNCTIONS OF THE COLON

• Absorption
  – Fluid & electrolytes
  – Bacterial fermentation products

• Transit of material to rectum

• Timely emptying of feces
  – Reservoir function
  – Defecation
HYPOTHETICAL MECHANISMS OF CONSTIPATION

• Excessive absorption rate
  – Never demonstrated

• Slow transit
  – “Colonic inertia”

• Impaired defecation
  – Capacious reservoir (megarectum)
  – Functional outlet obstruction
SLOW TRANSIT CONSTIPATION

• Predominant mechanism of severe infrequency in patients with idiopathic constipation
• Presumably a problem with colonic neuromuscular function or coordination
• Less common than once thought
• May be aggravated by functional outlet obstruction
• May be part of a generalized disorder
  – Chronic intestinal pseudo-obstruction
  – Hollow visceral myopathy
  – Enteric nervous system disorders
FUNCTIONAL OUTLET OBSTRUCTION

• May be sole cause of constipation or co-exist with slow transit constipation

• Many possible etiologies
  – Intrarectal intussusception
  – Anterior rectal wall ulcer syndrome
  – Perineal descent
  – Hirschsprung’s disease
  – Paradoxical puborectalis & external anal sphincter contraction during defecation (“dyssynergia,” “spastic pelvic floor,” “anismus”)

NORMAL PELVIC FLOOR FUNCTION

- Contraction of puborectalis muscle (pelvic floor) produces a 90° angle between the axis of the rectum and anal canal; provides continence for solids
- Contraction of external anal sphincter produces firm closure of anal canal and promotes continence for liquid stool and gas
NORMAL PELVIC FLOOR FUNCTION

- Relaxation of the puborectalis muscle and external anal sphincter allows straightening of the rectoanal angle and permits defecation.
SPASTIC PELVIC FLOOR SYNDROMES

• Psychiatric overtones
  – Physical and sexual abuse
  – Somatization syndrome
  – Malingering
  – Obsessive-compulsive disorder
  – Psychosis
  – Anxiety
IRRITABLE BOWEL SYNDROME WITH CONSTIPATION

• Overlap of normal transit constipation patients and IBS patients
  – Similar psychological profiles as other IBS patients
  – Similar problems with pain as other IBS patients

• Less clear how to classify these patients

• Not always distinguished in “constipation” trials
EVALUATION OF CONSTIPATION

• History
• Physical examination
  – Digital rectal examination
• Laboratory testing
  – Systemic diseases: thyroid, diabetes, hypercalcemia
• Imaging
  – Sigmoidoscopy
  – Barium enema
  – Colonic transit time (Sitz markers)
  – Defecography
OTHER TESTS

• Balloon expulsion
  – Used to evaluate outlet problems

• Anorectal manometry
  – Used to evaluate dyssynergia

• Electromyography
  – Used to evaluate dyssynergia
TREATMENT

• Treat underlying disorders
• Review medications and revise as needed
• Assess diet/fiber intake
• Laxatives
• Systemically-active agents (most not approved for treatment of constipation by FDA)
• Investigational agents with systemic actions
• Chloride-channel activator
• Biofeedback training (pelvic floor dysfunction)
• Surgery
DIET & FIBER

• Older individuals may decrease their overall food intake
  – This may reduce postprandial stimulation of colon motor activity (gastrocolic reflex)

• Fiber intake may be low
  – Difficulty in buying or preparing fruits & vegetables
  – Problems chewing
  – Rapid satiety

• Ideal fiber intake not defined in older population
  – Should aim for 20—30 g fiber per day
  – Excess fiber may accentuate bloating
LAXATIVES

• Drugs that alter stool composition or gastrointestinal motility to increase stool frequency or ease defecation
  – Bulking agents
    • Natural and synthetic fiber
  – Osmotic agents
    • Poorly absorbed ions, disaccharides/sugar alcohols
    • Polyethylene glycol
LAXATIVES

- Topically-active ("stimulant") agents
  - Detergents (docusates, bile acids)
  - Diphenylmethane derivatives (e.g., bisacodyl)
  - Ricinoleic acid (castor oil)
  - Anthraquinones (e.g., senna, cascara)

- Lubricant
  - Mineral oil
LAXATIVES

• Laxatives are best applied as part of a preventive program
• Goal should be production of 2—3 BMs weekly and control of secondary symptoms (bloating, discomfort)
• Osmotic laxatives currently favored, but may accentuate bloating
• Intermittent use of topically-active laxatives probably is safe
PROBLEMS WITH LAXATIVE THERAPY FOR CHRONIC CONSTIPATION

• Lack of effect on coexisting symptoms (e.g., bloating, incomplete evacuation, abdominal pain)
• Loss of effect with time
• Side effects
  – Bloating
  – Diarrhea
  – Electrolyte abnormalities
  – Melanosis
  – Fecal incontinence
• Toxicity
  – “Cathartic colon”
SYSTEMICALLY-ACTIVE AGENTS FOR CHRONIC CONSTIPATION

- Cholinergic agonists
  - Bethanechol*
  - Neostigmine*
- Prostaglandin agonist
  - Misoprostol*
- Colchicine*
- Opiate antagonists
  - Naloxone*
  - Naltrexone*
  - Methylnaltrexone*
  - Alvimopan*

*Not FDA-approved for treatment of chronic constipation
INVESTIGATIONAL SYSTEMIC AGENTS FOR CHRONIC CONSTIPATION

- 5-HT₄ agonists
  - Prucalopride
  - Renzapride

- Neurotrophic peptide
  - NT-3
POTENTIAL PROBLEMS WITH SYSTEMICALLY-ACTIVE DRUGS

• Unwanted effects elsewhere in the gut
• Systemic toxicity/side-effects
• Tachyphylaxis
• Lack of receptor sites/effector mechanisms in advanced disease
LOCALLY-ACTING THERAPY: Modulation of Chloride Channels
CHLORIDE CHANNELS OF THE GUT

- Chloride C-2 channel (ClC2)
  - Mainly concerned with regulation of tight junction permeability
  - Moderate capacity channel
  - Directly activated by lubiprostone from luminal side
- Cystic fibrosis transmembrane regulator (CFTR)
  - High capacity chloride channel
  - Mainly concerned with electrolyte transport (Cl secretion)
  - Activated by cAMP and cGMP
  - Linaclotide opens channel by increasing intracellular cGMP levels
LUBIPROSTONE

- Bicyclic fatty acid
- Prostaglandin derivative but does not interact with prostaglandin receptor
- Topical effect on C-2 chloride channels
- Mostly metabolized within gut; no detectable absorption of intact molecule (metabolite can be absorbed)
- Stimulates small bowel fluid and electrolyte secretion
- Motility stimulated
- FDA approved for chronic constipation and IBS-C in women
EFFECTIVENESS OF LUBIPROSTONE IN CHRONIC CONSTIPATION

Bowel movements per week

Intent-to-treat population

Baseline | Week 1 | Week 2 | Week 3 | Week 4

$P = 0.0001$ | $P = 0.0017$ | $P = 0.0002$ | $P = 0.0002$

$N = 242$

SIDE EFFECTS OF LUBIPROSTONE

- Nausea in ~30% of patients given 24 µg BID
  - Mitigated by giving drug with food or reducing dose
  - Drug discontinued in ~8% of patients for nausea
  - Less common in older patients (~12—19%)
- Headache, diarrhea, abdominal pain other side-effects
- Avoid if mechanical bowel obstruction, pregnancy
LINACLOTIDE

• Peptide analogue of guanylyn, a luminally-secreted peptide that modulates chloride secretion in the gut

• Activates guanylate cyclase C which opens CFTR chloride channel and increases chloride secretion
  – May also release cGMP into subepithelial space that may modulate enteric sensory nerve function

• Enhances secretion and transit

• Mostly metabolized within gut; no detectable absorption of intact molecule or active metabolites

• FDA approved for treating chronic constipation and IBS-C
LINACLOTIDE IN CHRONIC CONSTIPATION

SIDE EFFECTS OF LINACLOTIDE

• Diarrhea is most common side effect
  – Can be managed by lowering dose or frequency of dosing

• Not approved for patients <18 years old
  – Never use in children <6 years old
BIOFEEDBACK TRAINING

• In patients with pelvic floor dysfunction (i.e., anismus, puborectalis muscle relaxation failure) biofeedback training has been shown to reduce symptoms
• Patients are taught to relax the puborectalis muscle when straining to ease evacuation
• Repeated sessions over 2—4 weeks usually needed
• Limited availability outside of major motility centers
BIOFEEDBACK THERAPY FOR PELVIC FLOOR DYSSYNERGIA

- Patient views anorectal pressures generated during relaxing and squeezing pelvic floor muscles, emphasizing coordination
- Rapport with therapist is crucial to success
- Effects appear to be long lasting

52 patients receiving 5 weekly biofeedback sessions

Patient satisfaction at 6 months (%)

Pelvic floor dyssynergia: 71*
Slow transit: 8

*P = 0.001

SURGICAL MANAGEMENT OF CHRONIC CONSTIPATION

• Subtotal colectomy can improve stool frequency
• Candidates for colectomy need to be screened for outlet problems
• Patients with significant abdominal pain have more complications with postoperative small bowel obstruction
• Ileostomy is a less morbid option for higher-risk patients
PROSPECTS FOR THE FUTURE

• Better assessment of pathophysiology in individuals

• Therapy targeted at pathophysiology
  – New agents/techniques

• Preventive therapy
Thank you for your attention!

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