Irritable Bowel Syndrome: from pathophysiology to treatment

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Disclosures

- Shire
- Almirall
- Cephalon-Teva
- Mundipharma
- Mayoli Spindler
- Abbott
Irritable Bowel Syndrome

IBS cannot be resumed as colonic spasms occurring in patients with anxiety-depression and hypochondria.
Old concept

IBS is a motor disorder
Old concept: motility disorder

- Abnormal motility: non-specific
- Jejunum, ileum, colon
- Present in 40 to 50% of patients
- Therapeutic target: antispasmodic agents
  - "Ancient" drugs: 1980…
  - Poorly evaluated before launching
- Meta-analysis (poor quality of studies)
  - 3 positive, 1 negative
  - Decrease pain intensity: mebeverine, trimebutine, otilonium

Poynard et al, Aliment Pharmacol Ther 1994
Jailwala et al, Ann Intern Med 2000,
Lesbros-Pantoflickova et al Aliment Pharmacol Ther 2004
Reassessment of antispasmodic according modern criteria:

Chassany et al. Aliment Pharmacol Ther 2007

Phloroglucinol

Alverine Citrate + simethicone

Wittmann et al. Aliment Pharmacol Ther 2010

Other antispasmodics: generic drugs ➔ never reassessed!
New concept
IBS : a multifactorial pathology

Brain- gut axis disorder
IBS: a multifactorial pathology

Brain-gut axis disorder

Visceral hypersensitivity

Inflammation

Dysbiosis
Abnormal microbiota

Increase in intestinal permeability

Motor disorder
Visceral hypersensitivity

- Distension tests
  - Hypersensitivity
    - Lower pain threshold: 60 % of the patients
  - Allodynia + hypersensitivity
    - 80 % of the patients

Mertz et coll 1995
Where is the main abnormality?

Peripheral receptors:
- content
- permeability
- microbiota
- inflammation

Afferent nerves?

Medullar level?

Brain?

Sensori-motor reflex
Relationship between intestinal permeability and sensitivity to distension

Intestinal permeability

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Abdominal Pain

Score EVA (viscérale)

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Zhou et al. Pain 2009
Is IBS an inflammatory disorder?

- **Post-infectious IBS**:
  - Definition: onset of IBS symptoms after an acute bacterial gastroenteritis

- Symptoms occurrence: 6-12 months later

- Clinical manifestation:
  - Diarrhoea predominant IBS

- Main pathological abnormalities
  - Lymphocytes infiltration
  - Increase in mast cells
Increase in mast cells

- Jejunum
- Ileum
- Colon

Healthy subjects  IBS

Guilarte et al Gut 2007
Weston et al, Dig Dis Sci 1993
Barbara Gastroenterology 2004
Relationship between mast cells and pain

Barbara G et al, Gastroenterology 2006
Therapeutic consequences
Steroids

- Budesonide?
- No study.

Dunlop et al, Aliment Pharmacol Ther 2003
Randomized study vs. placebo
20 patients
Mesalasine 2.4 g/d, 8 weeks
No effect on symptoms
Decrease in inflammatory cells

Corinaldesi et al, Aliment Pharmacol Ther 2009
Microbiota

- There are more bacteria in the colon than cells in the whole organism

Rajilic-Stojanovic Gastroenterology 2011
Microbiota in IBS

• Recent data demonstrate that there is a dysbiosis in IBS patients
  – Mainly qualitative :
    • Microbiota composition is different in IBS in comparison to controls
      – Increase in firmicutes, decrease in bacteroidetes
      – But no specific profile
  – Also quantitative in some patients :
    • Increase in the total number of bacteria : small bowel bacterial overgrowth
      – Case-control study : RR = 3.45
Functional dysbiosis

Chassard C et al, Aliment Pharmacol Ther 2012
Consequences of this dysbiosis

• Poorly evaluated
• Main function of bacteria
  – Fermentation of non absorbable carbohydrates (starch, oligosaccharides)
  – Production of gas and short chain fatty acids
• In animal models, pronociceptive effects of
  – $\text{H}_2\text{S}$, $\text{CH}_4$
  – Butyric acid

Soret R et al, Gastroenterology 2012
Therapeutic consequences

- Effect on intestinal permeability
  - No drug available

- Dysbiosis
  - Probiotics
  - Antibiotics
Dysbiosis: probiotics

Mechanisms of action?
Regulatory effect on flora?
Anti-inflammatory effect?

Meta-analysis: RR 0.71 (IC95%: 0.57-0.88)
Number need to treat: 4 (IC 95%: 3-12)

O'Mahonny et al, Gastroenterology 2005
Moayyedi et al, Gut 2010
Bacterial overgrowth: antibiotic

- Rifaximin
- 550 mg x 3, 15 days
- Non constipated IBS
- 1260 patients
- Significantly better than placebo
  - Overall well being
  - Pain
  - Bloating
  - Delta: 9 to 10 %

Pimentel et al, NEJM 2011
Where is the main abnormality?

Peripheral receptors:
- content
- permeability
- microbiota
- inflammation

Afferent nerves?

Medullar level?

Brain?

Sensori-motor reflex
IBS: spinal hyperexcitability
2 patients over 3

Healthy subjects

IBS Patients

Coffin et al, 2004
Spinal hyperexcitability

- A reflect of diffuse hyperalgesia
- A marker of IBS severity
  - Facilitation: $381 \pm 46$
  - Inhibition: $310 \pm 63$
- Could explain associated comorbidities
  - Fibromyalgia…

Bouhassira et al, 2013
Brain control of visceral pain

- **Functional methods:**
  - Functional MRI
  - Pet Scan

- **Visceral stimulations:**
  - Activation of:
    - Thalamus
    - Orbito-frontal cortex
    - Insula and cingular cortex.
  - Control of pain and emotions

**Limbic system**

Moisset et al, Eur J Pain 2009
Pre-gabalin and rectal sensitivity in IBS

Responders: 57%
Progressive increase of doses → 150 à 450 mg/d
Poor tolerance!

Houghton et al, Gut 2007
Anti-depressive agents

- Mechanisms of action:
  - Central and peripheral modulation of pain control mechanisms.
  - Associated mood disorders: anxiety and depression
- Serotonin Reuptake Inhibitors:
  - Conflicting results
    - paroxetin, fluoxetine, citalopram
- Tricyclic agents: positive results
  - Imipramine, desipramine
    - Clinical studies
    - Mechanical studies
Anti-depressive agents

• Explain why!
  – Action on pain and not on psychic pain requiring psychiatric treatment….
  – Compliance ++++

• Prescription as in neuropathic pain
  – Low dosage : 25-50 mg imipramine
  – Progressive increase to limit side effects

• Efficacy :
  – Time required : 2-6 weeks
  – If efficient, duration of treatment : 6 months ?
Hypnosis

Pain

Bloating

Long term efficacy (18 months):

< 50 years: 95 %

> 50 years: 20 %

Whorwell PJ et al, Lancet 1984
Whorwell PJ et al, Gut 1987
Future ? Action both peripheral and on nerve afferences : Linaclotide

- Guanylate cyclase agonist
- IBS-C
- Phase III positive
- Mechanisms of action
  - Colonic secretion
  - Inhibition of colonic nociceptors in mice

Johnston, Gastroenterology 2010
Castro J et al, Gastroenterology 2013
Conclusion

• One IBS : No
• Different IBS : Yes
• Main difficulty : in a given patient, it is not possible to determine the main pathophysiological process and thus to use a specific and targeted treatment.
• Future :
  – Identify other mechanisms :
    • food (FODMAPS), bile acids…
  – Identify biological markers