腸易激綜合征的治疗策略

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腸易激綜合征
(Irritable bowel syndrome)

• Symptoms of recurrent abdominal pain or discomfort and a marked change in bowel habit for at least six months, with symptoms experienced on at least three days of at least three months. Two or more of the following must apply:

  • Pain is relieved by a bowel movement
  • Onset of pain is related to a change in frequency of stool
  • Onset of pain is related to a change in the appearance of stool
病理機制

Visceral Hypersensitivity
内脏高敏感性

Abnormal Gut Motility and Secretory Disorders
肠道蠕动异常及分泌紊乱

Autonomic Nervous System Dysfunction
植物神经系统功能紊乱

The neural, immunological, endocrine and metabolic pathways by which the microbiota influences the brain, and the proposed brain-to-microbiota component of this axis. Putative mechanisms by which bacteria access the brain and influence behaviour include bacterial products that gain access to the brain via the bloodstream and the area postrema, via cytokine release from mucosal immune cells, via the release of gut hormones such as 5-hydroxytryptamine (5-HT) from enteroendocrine cells, or via afferent neural pathways, including the vagus nerve. Stress and emotions can influence the microbial composition of the gut through the release of stress hormones or sympathetic neurotransmitters that influence gut physiology and alter the habitat of the microbiota. Alternatively, host stress hormones such as noradrenaline might influence bacterial gene expression or signaling between bacteria, and this might change the microbial composition and activity of the microbiota.
以腸道為主要靶點的藥物治療

- **Atypical benzodiazepine**
  - Modulates autonomic responses
  - Dextofisopam

- **K-Opioid receptor agonist**
  - Activates opioid receptors, which may elevate visceral sensation
  - Asimadoline

- **Dopaminergic antagonist**
  - Leads to prokinetic effects
  - Itopride

- **CFTR and chloride channel modulator**
  - *IBS-C: GC-C receptor agonists*
  - Linaclotide
  - Plecanatide
  - *IBS-C: chloride channel activator*
  - Lubiprostone
  - *IBS-D: chloride secretion inhibitors*
  - Crofelemer

- **Bile acid modulators**
  - Bile acids accelerate CTT, MI, & secretion
  - Chenodeoxycholic acid
  - IBAT inhibitor, A3309

- **Serotonin receptor modulator**
  - Agonist for *IBS-C*: accelerate GI transit & alter visceral sensation
  - 5HT_4 agonist: prucalopride, mosapride
  - Selective 5HT_4 partial agonist: tegaserod
  - Partial 5HT_3 agonist: pumosetrag

- **Antagonist for *IBS-D*:** slow GI transit and elevate visceral sensation
  - 5HT_3 antagonist: alosetron, ramosetron

- **Tryptophan hydroxylase-1 inhibitor**
  - GI level of serotonin
  - LX1031

- **CRF antagonist**
  - GI motility and visceral sensation
  - Pexacerfont
  - GW 876008

- **Oral carbon adsorbant**
  - Adsorbs luminal substances including serotonin and bile acids
  - AST-120
腸易激 + 腦易激（Irritable bowel + irritable brain?）
We found reasonable evidence to support the use of smooth-muscle relaxants for abdominal pain. In contrast, the benefits of bulking agents remain unproved despite a large number of trials. Loperamide seems to be effective for diarrhea. The potential efficacy of psychotropic agents should be confirmed in well-done, adequately powered trials. Newer agents, specifically 5-hydroxytryptamine–receptor antagonists, seem promising, but the amount of evidence to allow a definitive statement on their efficacy is insufficient at this time. Finally, the durability of treatment effects over longer intervals requires careful examination.
### 思維模式與藥物

#### Linear thinking model
- **Cause** → **Effect**

#### Circle thinking model
- **Cause** → **Effect** → **Cause**

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**One Drug for One Target for One Disease**

- Clear cause, with single target/pathway
- New drug development
- Bacteria-induced disease
- Peptic Ulcer

**Chinese medicine system**
- 3000+ years
- 100,000+ formulas
- Syndrome-based approach
- Personalized therapy
Very importantly: Stagnation of Liver and Deficiency of Spleen are the key mechanism of IBS, not just for the abdominal pain, diarrhea or constipation, and also the major reason for IBS recurrence.
中藥的特征-是多系統、多靶點、多途徑！
JCM16-02

Modification Based on Experience Consensus

Safety and Effectiveness

Mechanism

Patent Application

SFDA New Drug Development
1. 200+ classic formulas

2. Key—Important formula for painful diarrhea (IFPD)

3. Systematic review about IFPD effect for IBS patients-
   (Publication in J Altern and Complemt)

**Important Formula for Painful Diarrhea**
- *Rhizoma Atractylodis Macrocephalae* (Bai zhu/ 白朮)
- *Radix Paeoniae Lactiflorae* (Bai shao/ 白芍)
- *Pericarpium Citri Reticulatae* (Chen pi/ 陈皮)
- *Radix Saposhnikoviae* (Fang feng/ 防风)

Conclusion: There is evidence to indicate the potential usefulness of IFPD-A for IBS patients. The results were limited by the poor quality and heterogeneity of these studies. Further studies with carefully designed, randomized double-blinded placebo-controlled trials will be needed to confirm the effectiveness of IFPD or IFPD-A for IBS.
1. Why delete?
Pericarpium Citri Reticulatae（Chen pi/陈皮）and
Radix Saposhnikoviae（Fang feng/防风）

2. Why add?
Cortex Magnoliae Officinalis(Hou Po/厚樸)
Semen coicis Lachryma-jobi (yiyiren/薏苡仁)
Polygonaceae (Huo Tan Mu/火炭母)
Fructus Terminaliae Chebulae(he zi/诃子)
Rhizoma Corydalis Yanhusuo(Yan Hu Suo/延胡索)
Go through the case study in clinic

**Rhizoma Atractylodis Macrocephalae (Bai zhu/白朮)**
**Radix Paeoniae Lactiflorae (Bai shao/白芍)**
**Cortex Magnoliae Officinalis(Hou Po/厚樸)**
**Semen coicis Lachryma-jobi (yiyiren/薏苡仁)**
**Polygonaceae (Huo Tan Mu/火炭母)**
**Fructus Terminaliae.Chebulae(he zi/訶子)**
**Rhizoma Corydalis Yanhusuo(Yan Hu Suo/延胡索)**
Preclinical study about JCM 1602 effect

1. Analgesic effect in mice model

2. Anti-diarrhea effect in Castor oil-induced diarrhea and magnesium sulphate-induced diarrhea in Mice model
Finalization of JCM 1602 with fixed dosage

**Rhizoma Atractylodis Macrocephalae (Bai zhu/白朮)**
**Radix Paeoniae Lactiflorae (Bai shao/白芍 )**
**Cortex Magnoliae Officinalis(Hou Po/厚樸)**
**Semen coicis Lachryma-jobi (yiyiren /薏苡仁)**
**Polygonaceae (Huo Tan Mu/火炭母)**
**Fructus Terminaliae Chebulae(he zi/诃子)**
**Rhizoma Corydalis Yanhusuo(Yan Hu Suo/延胡索)**
Funding source and Team

- ITC of HKSAR
- Team
  - Faculty of Medicine/ CUHK
  - School of Chinese medicine/HKBU
Clinical Trial Design

Following Rome II criteria
Randomized double blinded placebo controlled study

- Barostat
- Functional MRI
- Gastroenterologists: symptom assessment & QOL

Run-in
- 2 weeks
- Placebo Herb + Placebo WM
- Herb + Placebo WM
- Placebo Herb + WM

Follow-up
- 8 weeks
- TCM Practitioners Physicians
實驗結果 Trial Results

- 8 weeks TCM > placebo > holopon
- 16 weeks TCM > placebo > holopon

- 系统思维方式与线性思维方式！
Patent

ZL2006-1-0146331.1

Rhizoma Atractylodis Macrocephalae (Bai zhu/白朮)
Radix Paeoniae Lactiflorae (Bai shao/白芍)
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Mechanism study design

- Post-infection IBS model
- Early life stress IBS model
Study design: JCM1602 for PI-IBS rats

- TNBS, i.col
- Saline, i.col

AWR test (4W post TNBS)

- water
- pCPA
- JCM 1.2 g/kg
- JCM 2.4 g/kg
- JCM 4.8 g/kg
- water

2 W treatment

- Visceral pain (AWR & EMG)
- EC cell number (Silver staining)
- 5-HT content (CE)
- TPH expression (Western blot), SERT expression (IHC)
Study design: JCM1602 for NMS rats

AWR test (4W post NMS)

- water
- Holopon 10 mg/kg
- JCM 2g/kg
- JCM 4g/kg
- JCM 8g/kg

AWR test (4W)

Normal control

2 W treatment

- Visceral pain (AWR & EMG)
- 5-HT content (Capillary electrophoresis)
- EC cell density/distribution (Silver staining)
- TPH expression (Western blot) SERT expression (IHC)
Effect of JCM-16021 on visceral hypersensitivity in PI-IBS rats

JCM-16021 attenuated visceral hyperalgesia in PI-IBS rats
JCM 16021 and visceral pain in NMS rats
JCM 16021 for Serotonin pathway
JCM-16021 對鈣通道的影響

水應激1小时內的糞粒數

離體腸道運動檢測

The effect on anti-diarrhea of the formula

vs.before treatment,
**p < 0.01, ***p < 0.001
JCM16021 对 MAPK pathway 的作用
JCM16021 的作用途徑

- Serotonin pathway
- MAPK pathway
- Calcium Pathway
- PAR-2 Pathway
- ......
IBS治療的變革

- 從臨床症狀層面，不僅要針對腸，還要針對腦；
- 從病理機制層面，不能只針對單一病理靶點，還需綜合考慮針對多系統病理通路
从传统多“靶點”出发

1、基於中醫理論指導

2、藥物作用“靶點”是針對不同的症狀特征的證候，所謂的“君臣佐使”，其作用靶點，有可能同一，如四君子湯的補氣(氣虛為君臣佐使的靶點)，有可能不同，如小承氣湯的熱結津傷(熱、結、津傷是靶點)等

3、傳統意義上的靶點，與現代藥理概念上的靶點並不一致，或者起碼在初始概念上並不一起,传统药物配伍并非针对靶点，虽然有可能有吻合

但是這種方薬的設計，特別是在療效驗證基礎上的方薬組合，為多靶點藥物治療的設計提供了可能
從傳統多“靶點”出發。。。

從以辨證論治為指導的“多靶點”方向，尋求藥物療效的最大化——理想複方

從系統生物學為指導，尋求疾病治療中病理環節的反映通路——治療靶向

從藥物化學為指導的有效組分分析——單體組合

三方面結合，一定能夠走出一條新藥研發路徑
JCM1602的方向：Version 2
綜合途徑

• 以證候為基礎的多靶點治療
• 以病理網絡為基礎的多通路探索
• 以藥物化學為基礎的成份分析
• 以線性思維與環性思維的結合

• 不只是治療腦與腸，應針對病理系統
• 不只是對IBS，系統病
• 。。。
致謝

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• RGC/GRF