OPIOID-INDUCED CONSTIPATION

DR ANDREW DAVIES
Introduction
Introduction

- Mean faecal weight 128 g / cap / day
- Mean range 51-796 g
- Absolute range 15-1505 g
- Main factors affecting mass are caloric intake, type of diet, body weight
- (Caloric intake accounts for ~ 28% variability)
Introduction

- 75% water
- 25% solids
- Organic (84-93% solids)
  - bacteria 25-54%
  - carbohydrate 25%
  - fat 2-15%
  - protein 2-25%
- Inorganic
  - calcium phosphate
  - iron phosphate
  - cells
  - secretions
Introduction
Introduction

Constipation

Opioids

Other causes

Functional constipation
Introduction

Opioid-induced constipation ≠

Functional constipation
Introduction

Mechanisms of OIC:

❖ Decreased small bowel motility
❖ Decreased water & electrolyte secretion small bowel
❖ Increased tone ileocaecal valve
❖ Decreased large bowel motility
❖ Increased water & electrolyte absorption large bowel
❖ Increased tone anal sphincter
❖ Reduced anorectal sensitivity (to distension)
Epidemiology
Opioids in chronic non-cancer pain: systematic review of efficacy and safety

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Non-malignant disease

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Opioid group</th>
<th>Placebo group</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>41%</td>
<td>11%</td>
<td>3.6 (2.7-4.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32%</td>
<td>12%</td>
<td>2.7 (2.1-3.6)</td>
</tr>
<tr>
<td>Somnolence / sedation</td>
<td>29%</td>
<td>10%</td>
<td>3.3 (2.4-4.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15%</td>
<td>3%</td>
<td>6.1 (3.3-11)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20%</td>
<td>7%</td>
<td>2.8 (2.0-4.0)</td>
</tr>
<tr>
<td>Itching</td>
<td>15%</td>
<td>7%</td>
<td>2.2 (1.4-3.3)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13%</td>
<td>9%</td>
<td>1.5 (1.0-2.1)</td>
</tr>
</tbody>
</table>
Non-malignant disease
DOI 10.1007/s00520-007-0373-1

ORIGINAL ARTICLE

Constipation in cancer patients on morphine

Joanne Droney · Joy Ross · Sophy Gretton ·
Ken Welsh · Hiroe Sato · Julia Riley
# Malignant disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number patients reporting no constipation</td>
<td>77 (28.5%)</td>
</tr>
<tr>
<td>Number patients reporting no constipation, and taking no laxatives</td>
<td>41 (15.2%)</td>
</tr>
<tr>
<td>Number patients reporting no constipation, and taking laxatives</td>
<td>36 (13.3%)</td>
</tr>
</tbody>
</table>
Opioid-induced constipation
Opioid-induced constipation
Diagnosis
Opioid-induced constipation

Rome IV criteria:
❖ New or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:
   a) straining during > ¼ (25%) of defaecations
   b) lumpy or hard stools (BSFS 1-2) > ¼ (25%) of defaecations
   c) sensation of incomplete evacuation > ¼ (25%) of defaecations
   d) sensation of anorectal obstruction/blockage > ¼ (25%) of defaecations
Opioid-induced constipation

Rome IV criteria:

e) manual manoeuvres to facilitate > ¼ (25%) of defaecations
f) fewer then 3 spontaneous bowel movements per week

❖ Loose stools are rarely present without the use of laxatives
Opioid-induced constipation

“A change, when initiating opioid therapy, from baseline bowel habits and defecation pattern that is characterized by any of the following:

a) reduced bowel frequency;
b) development or worsening of straining;
c) a sense of incomplete evacuation; or
d) patients’ perception of distress related to bowel habits”

Camilleri et al, 2014
Opioid-induced constipation

“The BFI is a simple assessment tool with a validated threshold of clinically significant constipation. Prescription treatments for opioid-induced constipation should be considered for patients who have a BFI score of ≥ 30 points and an inadequate response to first-line interventions.”

Argoff et al, 2015
Opioid-induced constipation

<table>
<thead>
<tr>
<th>Bowel Function Index (BFI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please complete all items in this assessment</td>
</tr>
</tbody>
</table>

1. Ease of defecation (NAS) during the last 7 days according to patient assessment:

| 0 = easy / no difficulty |
| 100 = severe difficulty |

**Ask the subject:** "During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"

**If the subject requires clarification, ask:** "During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"

2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment:

| 0 = not at all |
| 100 = very strong |

**Ask the subject:** "During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"

**If the subject requires clarification, ask:** "During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong."

3. Personal judgement of patient (NAS) regarding constipation during the last 7 days:

| 0 = not at all |
| 100 = very strong |

**Ask the subject:** "During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = "very strong"."

**If the subject requires clarification, ask:** "During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = "very strong"."
Clinical features
Opioid-induced constipation

- Abdominal pain
- Anorexia
- Early satiety
- Nausea
- Vomiting
- Abdominal distension
- Diarrhoea (“overflow”)

Opioid-induced constipation

- Flatulence
- Halitosis
- Heartburn
- Intestinal obstruction
- Intestinal perforation
- Anal fissure
- Haemorrhoids
Opioid-induced constipation

- General malaise
- Confusion
- Headache
- Pulmonary embolism
- Urinary retention
Opioid-induced constipation

- Psychological problems
- Social problems
- [Health economic burden]
Opioid-induced constipation

“...It's another stress.”

“I thought you would die, blow up inside, a couple of crazy things. Or [I thought I would] get infected or something would go wrong [with] one of your intestines.”

Dhingra L et al, 2012
Opioid-induced constipation

“When I am faced with taking a pain med, I will always think about the constipation that might result, and so I will try to take the smallest dose possible or do without”

Dhingra L et al, 2012
Opioid-induced constipation
Management
Opioid-induced constipation

- Lifestyle measures
- Conventional laxatives
- Rectal interventions
- Lubiprostone
- Prucalopride
- MethylNaltrexone
- Naloxegol
- Other PAMORAs
- Complementary therapies
- Opioid switching
“Correct position”

Correct position for opening your bowels

Step one
- Knees higher than hips

Step two
- Lean forwards and put elbows on your knees

Step three
- Bulge out your abdomen
- Straighten your spine

Correct position
- Knees higher than hips
- Lean forwards and put elbows on your knees
- Bulge out your abdomen
- Straighten your spine
Lubiprostone

- Oral chloride channel activator (CIC-2)
- Increases GI secretions
- "... is indicated for the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures (e.g., educational measures, physical activity) are inappropriate"
- Efficacy in non-malignant OIC
- (?) Efficacy in methadone induced constipation
Activation of CIC-2 channel leads to active secretion of Cl⁻ into GI lumen, which leads to passive para-cellular movement of Na⁺ (electro-chemical gradient) and water into GI lumen.

Increased intraluminal volume may stimulate stretch receptors, which may stimulate smooth muscle contraction (which may also have a therapeutic effect).
Lubiprostone

- 24 mcg twice a day
- Median time SBM – 23.5-28.5 hr
- Improvement in SBM (versus placebo)
- Improvements in other symptoms – straining, stool consistency
- GI adverse effects – nausea (9.9-16.8%), diarrhoea (9.6-11.3%)
- No effect on opioids
- Effective in functional constipation
- Approved OIC in USA
Prucalopride

- Oral 5-HT4 receptor agonist
- Increases GI motility
- "...is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief"
- Efficacy in non-malignant OIC
Stimulation of 5HT4 receptors increases GI motility via a number of different mechanisms.

Stimulation of epithelial 5HT4 receptors increases GI secretions (which may also have a therapeutic effect)
Prucalopride

- 2 mg once a day
- Improvement in SBM (versus placebo)
- Improvements in other symptoms – stool consistency
- GI adverse effects – abdominal pain (12.1%), nausea (~ 11.0%)
- No effect on opioids
- Effective in functional constipation
Methylnaltrexone
Methylnaltrexone

Relistor SPC:

Methylnaltrexone “is indicated for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older”.
Methylnaltrexone

Relistor SPC:

“Use of methylnaltrexone bromide in patients with known or suspected mechanical gastrointestinal obstruction, patients at increased risk for recurrent obstruction or in patients with acute surgical abdomen is contraindicated due to the potential for gastrointestinal perforation”.
Methylnaltrexone

Relistor SPC:

**Opioid - induced constipation in adult patients with chronic pain (except palliative care patients with advanced illness)**

“The recommended dose of methylnaltrexone bromide is 12 mg (0.6 mL of solution) subcutaneously, as needed, given as at least 4 doses weekly, up to once daily (7 doses weekly)”.

“In these patients, the treatment with usual laxatives should be stopped when commencing treatment with Relistor”.

Methylnaltrexone

Relistor SPC:

Opioid - induced constipation in adult patients with advanced illness (palliative care patients)

“The recommended dose of methylnaltrexone bromide is 8 mg (0.4 mL of solution) (for patients weighing 38-61 kg) or 12 mg (0.6 mL of solution) (for patients weighing 62-114 kg)”.

“The usual administration schedule is one single dose every other day. Doses may also be given with longer intervals, as per clinical need”.
Methylnaltrexone

Relistor SPC:

Opioid - induced constipation in adult patients with chronic pain (except palliative care patients with advanced illness)

“Patients may receive two consecutive doses 24 hours apart, only when there has been no response (bowel movement) to the dose on the preceding day”.

“In palliative care patients, Relistor is added to usual laxative treatment”.
Methylnaltrexone
Naloxegol
Naloxegol

Moventig SPC:

Naloxegol “is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s)”.

“To qualify as LIR, in the two weeks prior to first study visit patients had to have reported concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the pre-study period”.
Naloxegol

Moventig SPC:

“Patients with known or suspected gastrointestinal (GI) obstruction or in patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation”.

“Patients with underlying cancer who are at heightened risk of GI perforation, such as those with: underlying malignancies of gastrointestinal tract or peritoneum; recurrent or advanced ovarian cancer; vascular endothelial growth factor (VEGF) inhibitor treatment.”
Naloxegol

Moventig SPC:

“When naloxegol therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of naloxegol is determined”. 
Naloxegol

NICE technology appraisal guidance:

“Naloxegol is recommended, within its marketing authorisation, as an option for treating opioid induced constipation in adults whose constipation has not adequately responded to laxatives”.
Naloxegol

NICE technology appraisal guidance:

“An inadequate response is defined as opioid-induced constipation symptoms of at least moderate severity in at least 1 of the 4 stool symptom domains (that is, incomplete bowel movement, hard stools, straining or false alarms) while taking at least 1 laxative class for at least 4 days during the prior 2 weeks”.
Naloxegol (vs. methylnaltrexone):

- NICE approval
- Oral formulation
- (Daily treatment)
- Slower onset of action
- ? Less acute effects
- ? Less risk GI perforation
- Lower cost - £55.20 / 30 days vs £252.60 / 30 days (3 doses/week)
Other PAMORAs

- Naloxone (modified release formulation)
- Methylnaltrexone (oral formulation)
- Naldemedine – cancer data
- [Oxycodone / naloxone combination]
CANNON BALL MASSAGE.

CANNON BALLS are effective in combating certain forms of disease, as well as in destroying life. An eminent German physician discovered a few years ago that by means of a cannon ball covered with leather a patient suffering from inactive bowels may often effect a cure by the regular use of the cannon ball, rolling it along the course of the colon, beginning low down at the right side. This remedy has been in successful use for many years at the Battle Creek Sanitarium.

PRICE, by express, $1.75.
Petroleum jelly

Step 1: Roll Vaseline into balls

Step 2: Coat Vaseline balls with confectioners' sugar

Step 3: Freeze Vaseline balls

Step 4: Place next to Candy Jar
Conclusion
Conclusion

You will feel better
TOMORROW

If you take
Beecham's Pills
TONIGHT

Constipation may make you feel run-down and depressed. But Beecham's Pills act gently overnight — without gripping or strain. Take a dose of Beecham's Pills tonight — and for a few nights. You will be amazed how much better you feel — and how much better you look. 1/6d & 4d - a box, or three twists for 3d.

Beecham's Pills
Worth a Guinea a Box

YOU CAN NOW BUY THEM SMOOTH COATED
Conclusion

“...I'm already sick [with cancer]. I'm getting sicker [because of constipation] ”.

...It’s a contributor...I feel terrible, because it is contributing to my sickness”.