Opioid-Induced Constipation

Dr. Luigi Saita
Riabilitazione e Cura Palliative
Fondazione IRCCS Istituto Tumori
Milano

Clinicians don't ask, and patients don't talk”

Stein Kaasa

Budoni sabato 4/10/2008

Definition

"Constipation is the passage of small hard faeces infrequently and with difficulty.

Individuals vary in the weight they give to the different components of this definition when assessing their own constipation and may introduce other factors, such as pain and discomfort when defaecating, flatulence, bloating or a sensation of incomplete evacuation"

Larkin JP, et al. *Palliat Med.* 2008. Submitted

Definition

Severe opioid-induced constipation may limit opioid therapy, worsening analgesia

Thomas J. Et al NEJM May 29, 2008

Prevalence of symptoms in palliative care

%	Insomnia	Fatigue	Anxiety	Anorexia	Constip.	Dyspnea	Nausea	Vomiting	Depression
[1]Grond et al 1994	59	NA	NA	48	33	24	27	20	NA
[2]Potter et al 2003	NA	NA	13	34	32	31	29	16	NA
[3]Ström gren et al 2002	5	43	11	36	24	19	35	16	32
[4]Tsai et al 2006	54.9	95.8	73.5	84.3	76.1	42.3	53.5		69.6

O.I.C. prevalence

- Meta-analyses (11 studies): 41% of the 1025 patients in the studies[1]
- A survey of 2055 individuals using opioids to manage pain revealed that 57% reported constipation[2]
- About 40% of all patients on chronic opioid therapy[3]
- Up to 90% of cancer patients on chronic opioid therapy[3]

- 1. Kalso E, et al. Pain 2004:112:372-380.
- 2. Mangel A, et al. Aliment Pharmacol Ther. May 7, 2008
- 3. Thomas J. J Pain Symptom Manage. 2008;35:103-113.

Clinical Diagnosis

Usually underdiagnosed

Ask the patient systematically
bowel movements
stool characteristics
pain related to defecation

Physical examination

Radiological assessment

Impact

Often underestimated[1]

Part of a range of gastrointestinal symptoms[2]

Significant cause of distress[1]

Untreated complications affect patients life quality[1]

1. Mancini I, et al. Support Care Cancer. 1998;6:356-364.
2. Solano JP, et al. J Pain Symptom Manage. 2006;31:58-69.

Organic factors

Pharmacological agents: Antacids, anti-epileptics, anti-emetics (5-HT_3 antagonists), antihypertensives, antiparkinsonians, anticholinergics, antidepressants, antitussives, antidiarrhoeals (when used in excess), cancer chemotherapies (vinca alkaloids), diuretics (when causing dehydration), iron (orally administered), opioid analgesics, neuroleptics

Metabolic disturbances : Dehydration (fever, vomiting, polyuria, poor fluid intake, diuretics), hypercalcaemia, hypokalaemia, uraemia, hypothyroidism, diabetes

Neurological disorders : Cerebral tumours, spinal cord involvement, sacral nerve infiltration, autonomic failure (primary such as Parkinson's disease, multiple sclerosis, motor neurone disease; or secondary to cancer or diabetes)

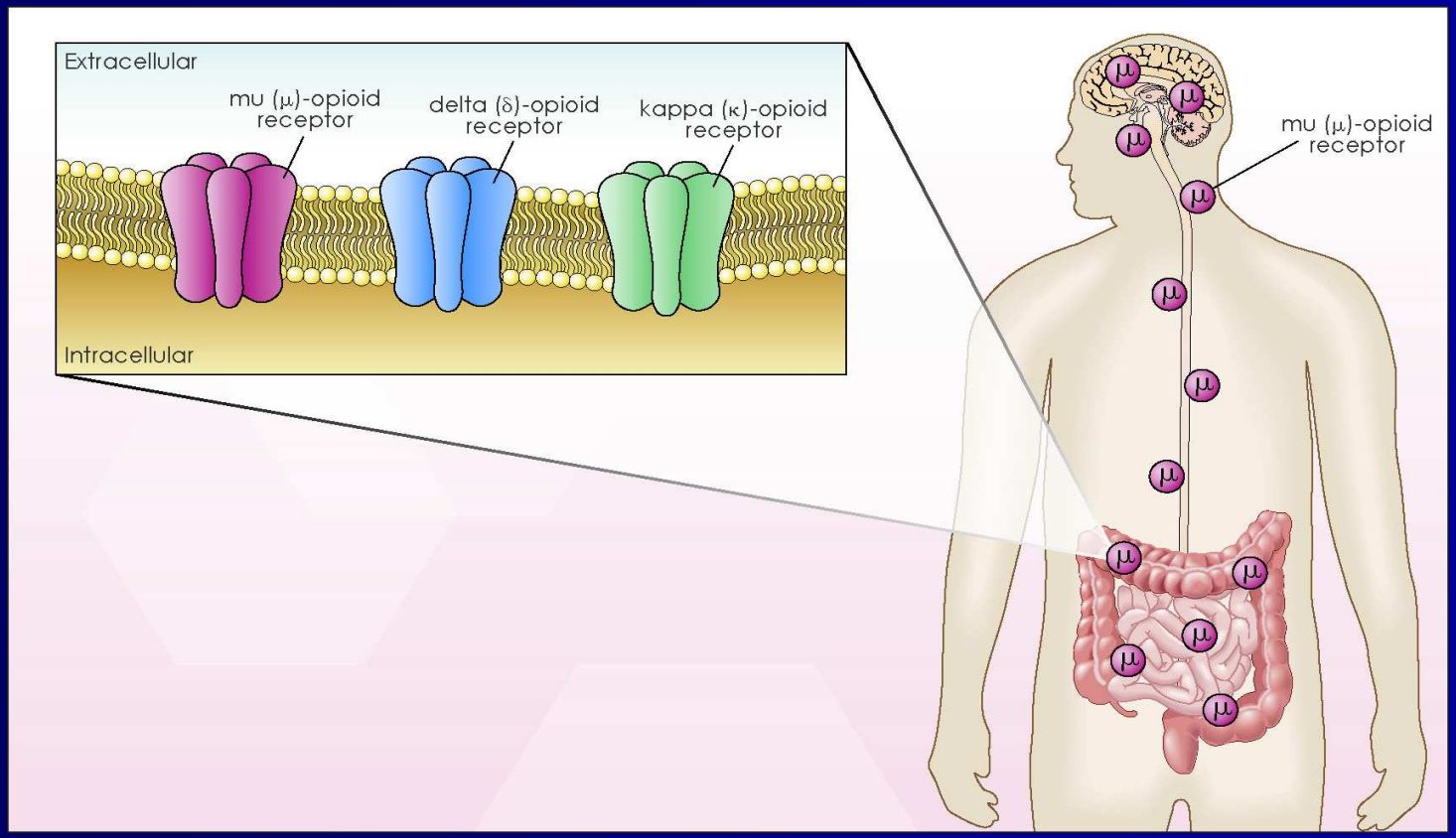
Structural abnormalities : Pelvic tumour mass, radiation fibrosis, painful anorectal conditions (haemorrhoids, anal fissure, peri-anal abscess), uncontrolled cancer-related pain or other pain such as movement-related pain or breakthrough pain

Functional factors

Diet ***Poor appetite and low amounts of food intake, low-fibre diet, poor fluid intake***

Environmental ***Lack of privacy, comfort or assistance with toileting***

Other factors ***Advanced age, inactivity, decreased mobility, confined to bed, depression, sedation***



De Schepper HU, et al. Neurogastroenterol Motil. 2004;16:383-394.

Bowel Movements Opioid Receptors

μ (mu)-opioid receptors:

Mediate analgesic effects of endogenous and exogenous opioids

Bowel dysfunction, euphoria and sedation

κ (kappa)-opioid receptors:

Analgesia, bowel dysfunction, sedation, increased diuresis

More prevalent in peripheral nerves than central nerves

Fewer CNS effects

δ (delta)-opioid receptors:

Analgesia

Mostly in central nervous system

Inhibit motility and secretion in GI tract

De Schepper HU, et al. Neurogastroenterol Motil. 2004;16:383-394.

Opioid-Induced Bowel Dysfunction

Opioids bind to opioid receptors peripherally and centrally

Central opioid receptors mediate analgesia, whereas stimulation of peripheral receptors delay GI transit time and reduce intestinal secretion

Opioids

- **suppress forward peristalsis**
- **raise sphincter tone**
- **increase fluid absorption**
- **reduce intestinal secretions**

McNicol E, et al. Cochrane Database Syst Rev. 2008;2:CD006322.

Current Treatment of Constipation

Behavior Modifications

- Promote adequate fluid intake
- Promote activity

Pharmacologic Treatments

- Laxatives

Rectal Interventions

Current Standards

Lactulose and Senna are commonly employed regimens

Movicol and co-danthramer

Laxatives should be co-prescribed with opioids

Laxatives should be titrated to individual patients and not to opioid dose

Enemas / suppositories / manual evacuation

Current Standards

One-third of patients with OIC have to be treated rectally

Uncomfortable for both patients and caregivers

Loss of control effects patient self-image

Tamayo AC, et al. Support Care Cancer 2004;12:613-618

recommendations

The EAPC has published recommendations[1,2] for treating constipation associated with opioids:

- ***Change opioid treatment***
- ***Non-pharmacologic strategies (e.g. dietary fibre, increased fluid intake)***
- ***Pharmacologic approaches (laxatives)***

54% of patients receiving laxatives to treat constipation do not achieve the "desired result"[3]

1. Hanks GW, et al. Br J Cancer. 2001;84:587-593.
2. Cherny N, et al. J Clin Oncol. 2001;19:2542–2554.
3. Pappagallo M. Am J Surg. 2001;182:11S–18S.

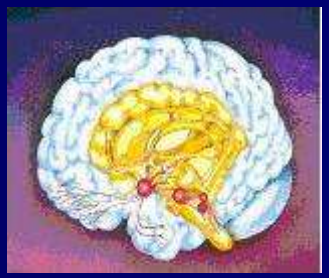
New strategy

"Previous studies have indicated that antagonism of mu-opioid receptors in the gastrointestinal tract may revers opioid induced gut hypomotility. The challenge has been to find compounds that can block peripheral receptors without inhibiting the central analgesic effects of opioids."

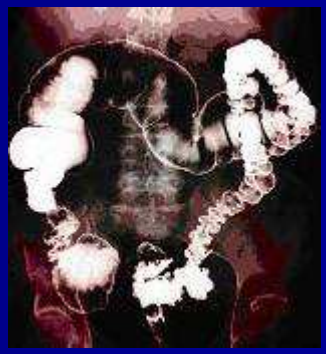
C. Berde. NEJM May 29 2008

Methylnaltrexone (MNTX): Peripheral Mu-Opioid Receptor Antagonist

Opioids activate receptors in the brain and provide pain relief…

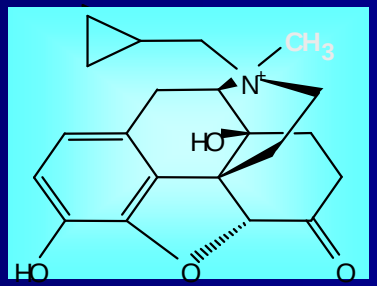


…but receptor activation in the GI tract results in constipation



Methylnaltrexone (MNTX): Peripheral Mu-Opioid Receptor Antagonist

Methylnaltrexone

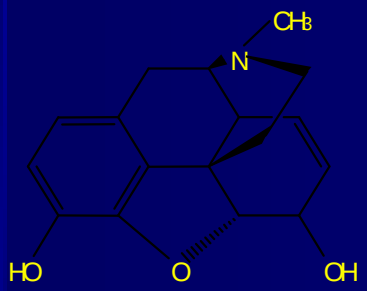


Selective peripheral antagonist
Restricted ability to cross blood-brain barrier

Methylnaltrexone (MNTX): Peripheral Mu-Opioid Receptor Antagonist

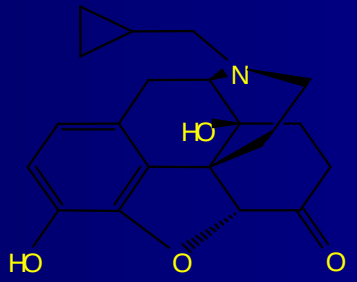
Subcutaneous Methylnaltrexone

- ***C_{max} ~ 0.5 hours***
- ***Restricted ability to cross blood-brain barrier***



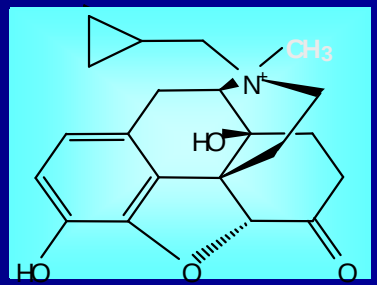
Morphine

Central and peripheral agonist



Naltrexone

Central and peripheral antagonist



Methylnaltrexone

Selective peripheral antagonist

Pain Assessment

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Assessment	Current Level of Pain* Mean ± SD		Worst Pain within 24 hours* Mean ± SD	
	Placebo (N=71)	Methylnaltrexone (N=62)	Placebo (N=71)	Methylnaltrexone (N=62)
Baseline	3.5 ± 2.6	3.6 ± 2.7	5.5 ± 2.6	5.1 ± 2.7
Day 1	3.6 ± 2.5	3.4 ± 2.3	5.6 ± 2.7	4.9 ± 2.2
Day 7	3.5 ± 2.6	3.4 ± 2.4	5.2 ± 2.6	5.2 ± 2.4
Day 14	2.7 ± 2.2	3.4 ± 2.6	4.8 ± 2.7	5.0 ± 2.5

Laxation Response

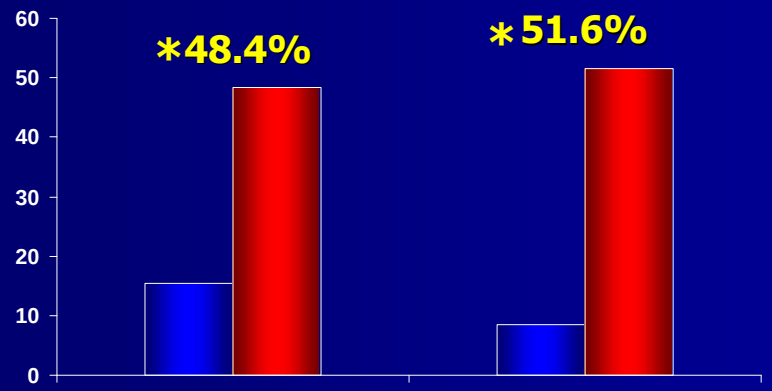
Thomas J. et al NEJM 29 May 2008

Co-primary endpoints:

- ***1. Rescue-free laxation response within 4 hours of first dose***
- ***2. Rescue-free laxation response within 4 hours after ≥2 of the first 4 doses***

*** P<0.0001 vs placebo**

% Patients with Laxation Response



Placebo (n=71)

Methylnaltrexone 0.15 mg/kg (n=62)

Laxation Response

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Secondary Endpoints:

- No signs of opioid withdrawal
- No change in pain scores

Mean Scores for Pain Assessment

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Assessment	Current Level of Pain* Mean ± SD		Worst Pain within 24 hours* Mean ± SD	
	Placebo (N=71)	Methylnaltrexone (N=62)	Placebo (N=71)	Methylnaltrexone (N=62)
Baseline	3.5 ± 2.6	3.6 ± 2.7	5.5 ± 2.6	5.1 ± 2.7
Day 1	3.6 ± 2.5	3.4 ± 2.3	5.6 ± 2.7	4.9 ± 2.2
Day 7	3.5 ± 2.6	3.4 ± 2.4	5.2 ± 2.6	5.2 ± 2.4
Day 14	2.7 ± 2.2	3.4 ± 2.6	4.8 ± 2.7	5.0 ± 2.5

Daily opioid dose (oral morphine-equivalent; mg/day)

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Study Day	Placebo (N=71)		Methylnaltrexone (N=63)	
	Median	Range	Median	Range
Baseline	**100.0**	10.0–10160.0	**150.0**	9.0–4160.0
1	**104.9**	5.0–12240.0	**157.5**	9.0–4160.0
3	**100.9**	10.0–16960.0	**160.0**	9.0–4160.0
5	**100.0**	10.0–16640.0	**180.0**	9.0–4774.0
7	**120.0**	10.0–23780.0	**180.0**	9.0–4714.0
9	**102.5**	10.0–28740.0	**180.0**	9.0–5382.0
11	**103.4**	10.0–2272.0	**180.0**	9.0–10966.0
13	**108.0**	5.0–1140.0	**90.0**	9.0–615.0

Adverse Events

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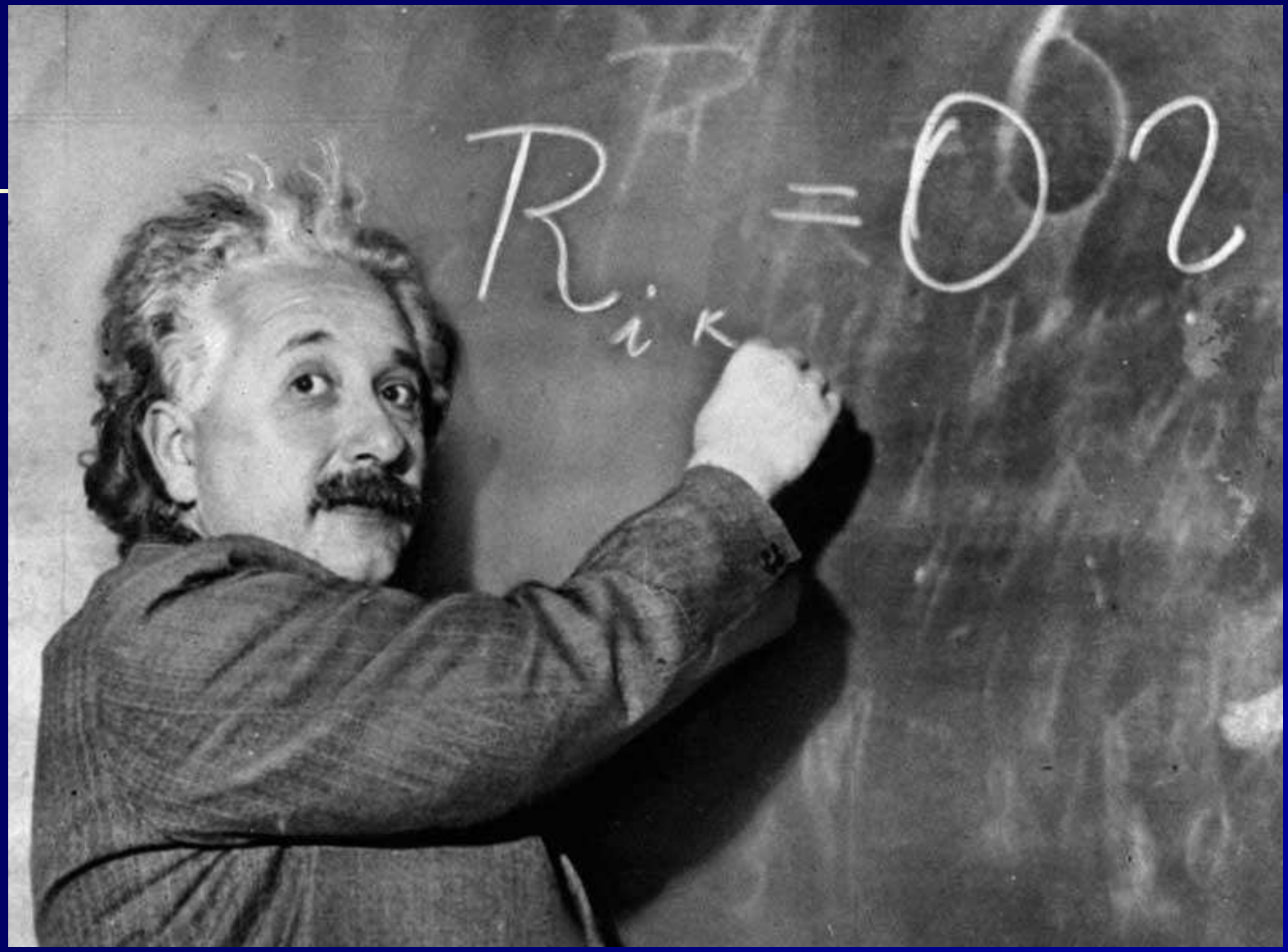
	Placebo*, n (%)	Methylnaltrexone*, n (%)
Patients with at least 1 AE	**57 (80.3)**	**51 (81.0)**
Abdominal pain NOS	**9 (12.7)**	**11 (17.5)**
Flatulence	**5 (7.0)**	**8 (12.7)**
Vomiting NOS	**9 (12.7)**	**8 (12.7)**
Malignant neoplasm progression	**9 (12.7)**	**7 (11.1)**
Nausea	**5 (7.0)**	**7 (11.1)**
Body temperature increased	**2 (2.8)**	**5 (7.9)**
Edema peripheral	**8 (11.3)**	**5 (7.9)**
Dizziness	**2 (2.8)**	**5 (7.9)**
Diarrhea NOS	**3 (4.2)**	**4 (6.3)**
Asthenia	**4 (5.6)**	**4 (6.3)**
Lethargy	**4 (5.6)**	**4 (6.3)**
Dehydration	**4 (5.6)**	**2 (3.2)**
Restlessness	**4 (5.6)**	**2 (3.2)**
Pain exacerbated	**7 (9.9)**	**2 (3.2)**
Abdominal distension	**6 (8.5)**	**1 (1.6)**
Abdominal tenderness	**4 (5.6)**	**1 (1.6)**
Somnolence	**4 (5.6)**	**1 (1.6)**
Fall	**7 (9.9)**	**1 (1.6)**
Tachycardia	**4 (5.6)**	**1 (1.6)**
Hypotension NOS	**4 (5.6)**	**0 (0.0)**

Alvimopan

Alvimopan is another peripherally constrained opioid antagonist that was developed for oral use.


$R_{ik} = 0$