Prevention and Treatment of Opioid Side Effects during Cancer Pain Management

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Outline

- Role of Opioids in management of Cancer Pain.

- Common Side Effects of Opioids:
  - Bowel issues (Constipation).
  - Somnolence and mental clouding.

- Less common Side Effects:
  - Nausea and vomiting.
  - Myoclonus
  - Opioid-induced Hyperalgesia
  - Respiratory depression
  - Pruritus
  - Allergic reaction
  - Urinary retention
Introduction

- Pain is highly prevalent in the cancer population.

- Patients with cancer experience **acute pain**, which may accompany surgery, invasive procedures, or complications e.g. pathological fracture.

- **Chronic pain** is experienced by:
  - 30 - 50 % of patients undergoing active anti-neoplastic therapy &
  - 75 - 90 % of those with advanced disease.

The causes of chronic pain are diverse, and both prevalence and severity vary with:
- the type of neoplasm,
- stage and extent of disease,
- prior treatment, co-morbidities, and other factors.

Tissue injury produced by the neoplasm is the primary etiology in about 75% of patients, and
- the remainder have pain related to the late effects of anti-neoplastic therapy or to painful co-morbidities.
Opioids are widely used for treatment of cancer pain because of their:

- safety,
- multiple routes of administration,
- ease of titration,
- reliability, and
- effectiveness for all types of pain (i.e. somatic, visceral, neuropathic).

Portenoy RK et al., UpToDate, last updated Dec. 2012
Opioids Side Effects

- Opioids can produce dose-limiting side effects:
  - constipation and mental clouding (most common).

- There is marked inter-individual variability in the sensitivity to such side effects:
  - due to genetic differences, age, co-morbidity, or interactions with other drugs.

- Effective treatment of side effects increases the likelihood of a favorable outcome.

Management of Opioid Side Effects

There are three approaches to treat opioid side effects:

i. Symptomatic management

ii. Dose reduction

iii. Changing to different opioid or route of administration.

Portenoy RK et al., UpToDate, last updated Dec. 2012
Opioids
Common Side Effects
"I stopped taking the medicine because I prefer the original disease to the side effects."

Side effects are a major contributor to the phenomenon of under-treatment of cancer pain.
**BOWEL ISSUES**

- Opioids affect gastrointestinal motility:
  - Constipation, bloating, early satiety, and pain.

- **Narcotic Bowel Syndrome:**
  - Abdominal pain & ileus.

- **Visceral Hyperalgesia:**
  - functional GI disorders
  - increased non-propulsive motility

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Grunkemeier DM et al., Clin Gastroenterol Hepatol 2007; 5:1126
CONSTIPATION

Opioid Side Effects
**CONSTIPATION**

- Constipation is the most common and persistent side effect from opioid analgesics*. 
- Constipation occurs in approximately 10 – 15 % of opioid-treated cancer patients. 
- It significantly impacts quality of life as well as opioid use patterns, resource utilization, and costs.

* Clemens KE, Klaschik E. Curr Opin Support Palliat Care 2008; 2:22
Constipation: Contributory factors 1

- Opioids bind to specific receptors in the GIT and CNS to reduce bowel motility by both direct and anti-cholinergic mechanisms.

- Longer GI transit time causes excessive water and electrolyte reabsorption from feces.

- Decreased biliary and pancreatic secretion further dehydrates stool.
Constipation: Contributory factors 2

- Concurrent use of other constipating drugs:
  - e.g. tricyclic antidepressants
- Dehydration.
- Advancing age.
- Immobility.
- Metabolic abnormalities:
  - e.g. hypercalcemia
- Chemotherapy:
  - Particularly the vinca alkaloids
- Tumor-related bowel obstruction.
Constipation

Opioid formulations

- Not all opioid formulations are equally constipating.
- The results of randomized trials are conflicting.
- Two systematic reviews* concluded that there is less constipation with transdermal fentanyl than with oral sustained release morphine.

**Constipation Prevention**

- All patients with predisposing factors should be considered for prophylactic laxative therapy when opioid treatment is started (Grade 2 C).

- Stool softener and contact cathartic e.g.
  - Docusate: 100 mg orally twice daily &
  - Senna: 2 tablets at bedtime

  OR

- Osmotic laxative e.g.
  - Lactulose: 30 ml daily OR
  - Polyethylene glycol: 2 tablespoons.

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Portenoy RK et al., UpToDate, last updated Dec. 2012
Constipation Management

- Assessment for alternative or contributory causes should be undertaken.

- This assessment includes:
  - history, physical examination (rectal examination),
  - laboratory evaluation,
  - imaging studies, or colonoscopy.

- Potentially treatable contributors to constipation should be managed appropriately.
Strategies for Management of Opioid-induced Constipation

I. Non-pharmacologic approaches for all patients (unless contraindicated by medical status):

- Increase fluid intake.
- Increase dietary soluble fiber.
- Encourage mobility.
- Ensure comfort and privacy for defecation.

*Portenoy RK et al., UpToDate, last updated Dec. 2012*
Strategies for Management of Opioid-induced Constipation

II. Select a Pharmacologic Strategy:

- **Intermittent* use of:**
  - rectal therapy: e.g. suppository or enema
  - osmotic laxative e.g. Mg OH, Mg citrate, Na phosphate
  - contact cathartic e.g. senna or bisacodyl

- **Daily use of:**
  - Stool softener e.g. Na docusate.
  - lactulose or sorbitol.
  - polyethylene glycol.

*Intermittent use = every 2-3 days
Strategies for Management of Opioid-induced Constipation

- Adjust dose of selected therapy to optimize effects.
- Switch or combine conventional approaches if initial therapy is inadequate.
- Refractory constipation:
  - Consider s.c. methylnaltrexone (Grade 1A) or alternative oral agent (naloxone or alvimopan).
  - Manual disimpaction: (provided there is no evidence of bowel obstruction or ileus)

Candy B et al., Cochrane Database Syst Rev, 2011
SOMNOLENCE & MENTAL CLOUDING

Opioid Side Effects
SOMNOLENCE & MENTAL CLOUDING

- Opioid can cause sedation and cognitive impairment.
- Symptoms wane over a period of days or weeks.
- Cognitive impairment ranges from:
  - slight inattention or fatigue, to disorientation, severe memory impairment, or extreme confusion and delirium.
- Perceptual disorders range from:
  - increased dreaming and illusions to frank hallucinations,
- Mood disturbance is more often:
  - negative (irritability, depressed mood, dysphoria) than
  - positive (contentment, euphoria).
SOMNOLENCE & MENTAL CLOUDING
Management

- Obvious contributing causes should be treated:
  - e.g. primary CNS pathology, metabolic disturbances, dehydration.

- Nonessential centrally-acting medications should be reduced or eliminated.

- The opioid regimen should be evaluated:
  - If analgesia is satisfactory: reduce the dose.
  - if analgesia is unsatisfactory: opioid rotation may be tried, or an adjuvant (co-analgesic) may be started to achieve an opioid-sparing effect.
III- SOMNOLENCE & MENTAL CLOUDING

Management: Psychostimulants, 1

- **Methylphenidate**
  - Starting dose: 5 mg in the morning and at noon.
  - Titrate dose until benefits or side effects occur (anxiety, hallucinations and sweating).

- **Modafinil**
  - Is a non-amphetamine psychostimulant,
  - It causes fewer sympathomimetic side effects than other psychostimulants.
  - Initial dose: 100 to 200 mg/day.

Grade 2B
Relative contraindications include:
- preexisting anorexia, severe insomnia,
- a psychiatric disorder,
- significant cardiac disease, or
- poorly controlled hypertension.

Older patients and those with early dementia are susceptible to untoward psychotomimetic and cognitive disturbance.

The therapeutic effects of psychostimulants sometimes wane over time.
Opioids

Less common Side Effects
Opioids
Less common Side Effects

1. Nausea and vomiting.
2. Myoclonus
3. Opioid-induced Hyperalgesia
4. Respiratory depression
5. Pruritus
6. Allergic reaction
7. Urinary retention
1- Nausea and vomiting

- Nausea is a frequent side effect of opioid therapy, but tolerance occurs quickly.
- Gradual increase of opioid dose may prevent persistent nausea.
- Persistent nausea often occurs in the context of other GI symptoms such as reflux, anorexia, early satiety, and abdominal bloating.

Opioid Side Effects
Nausea and vomiting

Mehanisms

- Opioids have three emetogenic mechanisms:
  i. a direct effect on the chemoreceptor trigger zone,
  ii. enhanced vestibular sensitivity, and
  iii. delayed gastric emptying.

- Refractory constipation and stool impaction may be contributory.
  - When present, they should be managed first.
Nausea and vomiting
Management

- Chronic nausea usually responds to drug therapies used for acute nausea.

- First line agents include:
  - Dopamine antagonist e.g. prochlorperazine or
  - Metoclopramide (also a prokinetic drug), or
  - Serotonin receptor antagonist e.g. ondansetron.

- Opioid rotation or a change in route of administration (s.c.) could be considered.

Hardy J et al., Support Care Cancer, 2002
2- Myoclonus

- Myoclonus is uncontrollable spasm of certain muscle groups.
- It is a common dose-related effect of opioids that is often associated with somnolence & mental clouding.
- The etiology may be multifactorial, with contributions from other drugs and/or metabolic disturbances.

Myoclonus Management

- Low-dose of the benzodiazepine e.g.
  - Clonazepam (0.5 mg orally every 6 – 8 hours) or
  - Lorazepam (0.5 – 1 mg sublingually or IV q 1 to 2 hours).

- Opioid rotation.

- Addition of adjuvant analgesic to reduce opioid dose.

- Anticonvulsant (rarely considered).
3- Opioid-induced hyperalgesia (OIH)

- It is a state of nociceptive sensitization that is caused by exposure to opioids.

- It is characterized by a paradoxical response whereby a patient receiving opioids for treatment of pain may actually
  - become more sensitive to certain painful stimuli &
  - experience pain from non-painful stimuli (allodynia).

- OIH usually linked to the development of analgesic tolerance.

**When suspected, consider opioid rotation or use of a non-opioid strategy for pain control.**

4- Respiratory depression

- Respiratory depression is a serious adverse effect of opioids.

- Tolerance usually develops rapidly to this effect.

- Cautious selection of the initial dose & conservative incremental dose titration limit the risk of respiratory depression.

Respiratory depression
Contributing factors

- Rapid titration.
- Sleep apnea syndrome.
- Other serious cardiopulmonary co-morbidity that limits ventilatory reserve.
- Combination with a sedative-hypnotic.
Respiratory depression
Management

- If hypoventilation and moderate sedation occur:
  - withhold further opioids until respiratory rate rises or pain returns.

- Naloxone should be reserved for:
  - symptomatic respiratory depression or
  - progressive obtundation.

- Use small bolus injections of dilute solution:
  - 1 mL doses of a 0.4 mg diluted in 10 mL saline,
  - titrate against respiratory rate.
Respiratory depression
Management, Naloxone

- Repeated doses are often necessary as naloxone's half-life is shorter than that of most opioids.

- Naloxone infusion may be required in patients receiving sustained-release opioid formulations or long half-life drugs (e.g. methadone or levorphanol)
5- Pruritus

- It is observed in 2 – 10 % of patients receiving chronic opioids.

- The exact mechanism is uncertain.

- Morphine is reported to cause histamine release from mast cells,
  - other opioids (i.e. fentanyl, sufentanil, and oxymorphone) are less likely to produce histamine release, they still associated with pruritus.

- There is evidence that opioid-induced pruritus is mediated through central mu opioid receptors*.

* Ko MC et al., J Pharmacol Exp Ther, 2004
Pruritus Management

- Antihistamines are commonly used as first-line agents, with varying degrees of success.

- Another option is opioid rotation.

- Low doses of opioid antagonists are effective for treatment of pruritus in the postoperative setting, without reversal of opioid analgesia
  - e.g. nalmefene 10 to 25 mic IV, nalbuphine 1-5 mg IV/IM.

Ganesh A, Maxwell LG. Drugs, 2007
6- Allergic reaction

- True opioid allergy is very rare, but both contact dermatitis and systemic hypersensitivity have been reported.

- For allergy to morphine or a semisynthetic opioid (e.g. hydromorphone or oxycodone) consider
  - one of the synthetic opioids (e.g. fentanyl or methadone), along with
  - co-administration of antihistamine and a glucocorticoid.
7- Urinary retention

- Mechanism include both:
  - A peripheral effect on nerves that innervate the bladder increasing the tone of the urinary bladder sphincter &
  - Direct binding to spinal opioid receptors causing total bladder relaxation.

- Relieve acute urinary retention by catheterization of the bladder.

- Reduce the dose of drugs that may contribute to urinary retention, such as anticholinergic drugs.
Urinary retention Management

- Naloxone is effective in reversing urinary retention, but also reverses analgesic effect in postoperative setting.
- Nalbuphine was effective at reversing the urinary retention with sustained analgesic effect in the postoperative setting.
- Some patients appear to respond to drugs used to treat urinary retention due to prostatic hypertrophy
  - e.g. alpha-1 blockers doxazosin or tamsulosin.
Conclusion

- Opioid therapy is the first-line approach for moderate or severe chronic cancer pain.
- Opioids can produce dose-limiting side effects, the most common of which are constipation and mental clouding.
- Effective treatment of side effects increases the likelihood of a favorable outcome.
Be Cautious Of The Side Effects

Thank you