Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

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Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

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Part 2
Managing Postoperative Ileus
Robert MacLaren, Pharm.D., FCCM, FCCP

Part 3
New and Emerging Options for Managing Postoperative Ileus: Clinical Research and Potential Implications for Pharmacists
Michael D. Kraft, Pharm.D.

P R O G R A M   F A C U L T Y

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Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

PROGRAM OVERVIEW

One of the most common causes of extended length of hospital stay following abdominal surgery is postoperative ileus (POI), which is temporary impairment of gastrointestinal motility characterized by delayed passage of gas and stool, as well as by abdominal pain, nausea and vomiting, and diminished appetite. Preventing or minimizing postoperative ileus is an important aspect of perioperative care because the condition may delay patient ambulation, increasing the risk for pulmonary and thromboembolic complications; POI can also delay enteral feedings or resumption of a solid diet, resulting in poor nutrition with delayed wound healing. The use of opioid analgesics for postoperative pain often exacerbates POI.

While a cure for postoperative ileus has not yet been found, current management strategies use a multimodal approach consisting of careful selection of anesthesia and analgesic regimens, early mobilization and institution of enteral nutrition, and avoidance of nasogastric tube placement. Ongoing clinical research continues to evaluate the effectiveness of these management strategies, as well as to explore new and emerging pharmacologic options like μ-opioid receptor antagonists.

Using a case-based format, this symposium will provide an overview of postoperative ileus, including its multifactorial etiology and impact on patient and economic outcomes. Current treatment options for POI will be presented, focusing on the role of health-system pharmacists in the multidisciplinary care of perioperative patients. The results of current clinical research exploring new and emerging pharmacologic options for preventing and managing postoperative ileus also will be presented. By being aware of POI, its ramifications, current management strategies, and emerging therapies, health-system pharmacists will not only be able to provide high quality patient care for postoperative patients but also assume a leadership role on the multidisciplinary team responsible for establishing therapy guidelines during the perioperative period.

PROGRAM OBJECTIVES

At the conclusion of this program, participants should be able to

- Describe the pathophysiology of postoperative ileus (POI).
- Identify at least three clinical and economic consequences of POI.
- Describe the rationale for at least three components included in the multimodal approach for managing POI.
- Describe the role of health-system pharmacists in preventing and managing POI.
- Given pertinent patient information, recommend strategies for preventing or minimizing the impact of POI.
- Describe recent clinical research into new and emerging pharmacologic options for preventing and managing POI.
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CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The program provides 2.5 hours (0.25 CEUs) of continuing education credit (program number 204-000-07-450-H01P).

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This activity consists of audio, post-test, and activity evaluation tool. Participants must listen to the entire presentation, take the activity post-test, and complete the course evaluation to receive continuing education credit. A minimum score of 70% is required on the test for credit to be awarded, and participants may print their official statements of continuing education credit immediately. The estimated time required to complete this activity is 2.5 hours. This activity is provided free of charge.

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Multimodal Approach for Managing Postoperative Ileus: 
Role of Health-System Pharmacists

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Brian L. Erstad, Pharm.D., is Professor in the Department of Pharmacy Practice and Science at The University of Arizona College of Pharmacy in Tucson. He carries out his clinical responsibilities at the University Medical Center in Tucson, where he is a member of the nutritional support team. Dr. Erstad also is on the faculty for the Center for Health Outcomes and PharmacoEconomic Research in the College of Pharmacy.

Dr. Erstad earned his Bachelor of Science degree in pharmacy from South Dakota State University and then worked as a staff pharmacist for approximately eight years in community hospital practice. He subsequently earned his Doctor of Pharmacy degree from The University of Arizona and completed a residency at the University Medical Center in Tucson. Dr. Erstad also graduated from the Arizona Clinical Research Training Program, which was funded by an NIH K30 Clinical Research Curriculum Award. His research interests pertain to critical care medicine with an emphasis on blood product derivatives, blood conservation strategies, infectious diseases, and related outcomes. He has authored more than 100 peer-reviewed articles and book chapters.

Dr. Erstad is a board-certified pharmacotherapy specialist, and he has received recognition as a Fellow by the following organizations: American College of Critical Care Medicine, American Society of Health-System Pharmacists, and the American College of Clinical Pharmacy. He has received the ACCP Clinical Practice Award for substantial and outstanding contributions to clinical pharmacy practice, and, in October 2007, he received the ACCP Education Award.
Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

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Presentation

Postoperative Ileus: A Multifaceted Health Problem

Abstract

The role of the pharmacist has evolved throughout history from an initial focus on the product through the trading and selling of drugs to the current focus on the patient with interdisciplinary practice models. In the health-system setting, pharmacists are involved in the choice of medications for formularies, medication-use evaluations, clinician and patient education regarding medications, specialized clinical teams dealing with medications and nutrition support, and research activities.

The pharmacists’ involvement in all of these areas is important as new therapies are investigated that are intended to prevent the complications associated with postoperative ileus (POI). A general knowledge of gastrointestinal tract anatomy, physiology, and function is necessary for understanding the actions of medications currently under development. To complicate matters, the terminology associated with POI has changed over time. Currently, POI refers to a non-mechanical obstruction or dysfunction that lasts beyond the normal time to return to full function after a major stressful event, such as surgery. The pathophysiology and causes of POI are multifactorial, and the signs and symptoms may vary substantially. There is no single diagnostic test for POI or for defining when gastrointestinal function has returned as POI resolves. The health care burden associated with POI is substantial, so it is important to identify and ameliorate causative or aggravating factors, such as opioid analgesics.

Learning Objectives

At the conclusion of this presentation, participants should be able to

- List three classes of medications that decrease gastrointestinal propulsive movements or motility.
- Describe the normal anatomy and physiology of the gastrointestinal tract.
- List the order in which organs of the gastrointestinal tract return their function as postoperative ileus resolves.
- Describe how ileus differs from obstruction.
- Describe how postoperative ileus is usually diagnosed.
- Discuss the difficulties in documenting the resolution of postoperative ileus.
Postoperative Ileus: A Multifaceted Health Problem

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Pharmacy Then and Now
Several medications are at various stages of development for use in reducing the duration of postoperative ileus (POI). In addition to the role of the pharmacist in drug development, what roles are there for pharmacists as the drugs near approval and after they are released?

Pharmacy Then
• Apothecarius referred to in 10th century
• Trading in spices and drugs in London in 11th century taken over by grocers
• By 12th century, some healers focused on drugs (apothecaries)
• New profession: barber surgeons

New Profession circa 1960s: Butcher Barbers

Turf Battles: 13th Century
• 13th Century: distinction between physicians and apothecaries for first time
  – Only physicians allowed to administer therapies or counsel patients
  – Surgeons could perform manual tasks (phlebotomy); apothecaries could dispense
• 16th – 17th Century: apothecaries and grocers united, then later separated

Apothecary
“Even into the sixteenth century, the apothecary was legally required to maintain the following in stock: wood lice, rain worms, ants, vipers, scorpions, frogs and crabs; also the skull of a dead person who was not buried, the bone from the heart of a bat, sparrow brains and hare brains, teeth of wild pigs and elephant skin, frog hearts, fox lungs, wolf intestines, human fat, and so on”

Institute of Medicine

- To Err is Human: Building a Safer Health System
- Crossing the Quality Chasm: A New Health System for the 21st Century
- Preventing Medication Errors

- Interdisciplinary effort with interdisciplinary recommendations for education and practice

"Just give what I ordered…"
"Physicians who need me the least…"

Pharmacy Now

- Pharmacy and therapeutics (P&T) committee involvement including pharmacoeconomic analyses
- Evaluations (e.g., medication-use evaluations) of agents used
- Clinician and patient education with recommendations regarding medications that may cause or aggravate POI
- Nutritional support recommendations
- Participation in research activities

P&T Involvement

- Pharmacist involvement either on P&T committees or for expertise with specific drugs
- Increasing use of pharmacoconomics by P&T committees
  - Survey of pharmacy directors
    - 92.1% of respondents indicated pharmacoeconomic analyses were used in formulary management process
    - 66% indicated quality of life (QOL) information was used


Evaluations

Approximately 3-month evaluation of metoclopramide use in medical and surgical intensive care units

Mean time to first bowel movement 1.7 ± 1.4 days
Mean duration of therapy 10.7 ± 7.1 days
Mean duration of therapy for ileus 11.5 ± 7.3 days


Education on Medications

- Sympathomimetics decrease propulsive contractions and tone through alpha and beta receptors
  - e.g., dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine
- Opioids decrease propulsive contractions and increase nonpropulsive contractions especially in upper gastrointestinal (GI) tract
  - e.g., morphine, meperidine, fentanyl
- Miscellaneous drugs suppress motility
  - e.g., anesthetics, atropine, calcium channel antagonists, clonidine, loperamide, phenothiazines, somatostatin (octreotide) in higher doses?, tricyclic antidepressants


Education on Medications

Most of the following cause adverse effects on GI tract, often as extensions of pharmacologic actions

- Antibiotics
  - Allow selective increase in bacteria
- Sorbitol (drug product additive), lactulose
  - Osmolar laxatives
- Antacids (e.g., magnesium as poorly absorbed cation)
- Other laxatives
  - Varying mechanisms
Nutritional Support

- Oral and nasoenteral (ND or NJ) feedings
- Systematic review and meta-analysis of randomized controlled trials comparing nothing by mouth vs. feedings within 24 hours of elective surgery
- Primary outcomes in favor of early feedings: anastomotic dehiscence (RR= 0.53, 95% CI= 0.26 to 1.08), infections (RR= 0.72, 95% CI= 0.54 to 0.98)
- Incidence of vomiting was higher in feeding group (RR= 1.27, 95% CI= 1.01 to 1.61)
- Indirect evidence that ileus is reduced with early feedings but influence of pain control not studied


Research

Multiple Logistic Regression Analysis of Bowel Movements and Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
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<td>26.599</td>
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<tr>
<td>Prokinetic</td>
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<td>0.694-28.19</td>
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<td>Docusate</td>
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<td>Apache II</td>
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<td>Diet</td>
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<td>0.124-5.957</td>
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<td>Log. Morphine</td>
<td>0.756</td>
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<td>Gender (male)</td>
<td>0.699</td>
<td>0.137-1.053</td>
<td>0.667</td>
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<tr>
<td>Vasopressors</td>
<td>11.097</td>
<td>1.102-111.72</td>
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Ileus: Case Report

- 63-year-old man s/p bowel resection has been receiving morphine 4 mg/hr for three days by patient-controlled analgesia (PCA)
- Began on PCA morphine one week ago with 2 mg i.v. bolus with 10-minute lock-out interval
- Patient started oral feedings today
- M.D. wants to convert patient to oral medications and discharge tomorrow

Options

- Take an extended lunch break and hope the patient gets transferred to another hospital
- Say you’re sick and go home
- Dump it on the new hire
- Dump it on the student
- Just do it, because that’s what the shoe commercial says

Gastrointestinal Anatomy and Physiology

- Stomach
- Small intestine
- Large intestine

Stomach
Gastrointestinal Control

Interactions of various components
• Neuronal
• Hormonal
• Mechanical
• Immunomodulation

Neuronal

• Acetylcholine and norepinephrine key roles
• Extrinsic nervous system in continuous communication with intrinsic system
• Intrinsic (enteric) nervous system
  – Nerve cell bodies grouped into ganglia
  – Ganglia connected to form plexuses (network)
  – Auerbach’s (myenteric) plexus
  – Meissner’s (submucosal) plexus
  – Nonganglionated plexuses

Hormonal

Gastrointestinal peptides
• Affect blood flow, motility, secretions
• Some act as growth factors
• Some mediate signals to central nervous system

Hormonal

• Endocrine peptides: secreted in blood
  – Cholecystokinin, gastrin, gastric inhibitory polypeptide, glucagon, insulin, motilin, neurotensin, peptides YY, secretin, somatostatin, urogastrone
• Neurocrine peptides: affect cells in contact with nerve terminals
  – Multiple, including calcitonin gene-related peptide, cholecystokinin, galanin, motilin, neurotension, neuropeptide Y, pancreastatin, peptides HM and YY, opioids, somatostatin, substance P, vasoactive intestinal peptide (VIP)
• Paracrine peptides: affect local cells (more widespread than neurocrine, less than endocrine)
  – Peptide YY, somatostatin
Mechanical
• Propulsion and mixing, hopefully well-coordinated
• Varies in fed versus fasting states and after stressful events, such as surgery
• Smooth muscle regulated by
  – Calcium and contractile proteins
  – Electrical, neurohormonal regulation
  – Humoral factors produced by smooth muscle (adenosine, eicosanoids, histamine, serotonin)

Immunomodulation
• Complex interactions between brain and gastrointestinal tract
• Gastrointestinal tract must be able to differentiate beneficial substances from infectious and toxic substances
• Gut-associated lymphoid tissue (GALT) has developed specific adaptive properties to deal with this differentiation
• Prostaglandins and cytokines secreted

Ileus
• Ileus- Greek for twisted
• Until late 19th – early 20th century, the term “ileus” was ill-defined
• Often referred to intussusception, volvulus
• Term now refers to non-mechanical obstruction (dysfunction but surgery not needed)
• Usual return of GI function (longer if abdominal/pelvic)
  – Stomach 24-48 hours
  – Small bowel 12-24 hours
  – Colon 48-72 hrs

Ileus
Intestinal transit time can be measured (usually for research purposes)
• Scintigraphy
• Radiopaque markers
• Nonabsorbable markers
• Passage of $^{51}$Cr$^3$ in stool
• Less invasive or non-radiation measurements
  – Food coloring
  – Lactulose breath hydrogen testing

What Ileus Isn’t
Constipation vs. Ileus: Terminology
Constipation: inability to pass feces easily
“Golden age of purgation in 1920–1930s”
• Enemas
• Irrigations
• Stimulators
• Abdominal massage
• Abdominal support belts
• Rectal dilators

### Small Bowel Obstruction (SBO)
- Approximately 60% of cases associated with adhesions secondary to abdominal or pelvic surgery (upper GI less common)
- Others due to cancer, Crohn’s disease, and hernias
- May be partial or complete; strangulation is life-threatening form of SBO
- Both CT and ultrasound have very high specificity; CT somewhat higher sensitivity
- Treatment
  - Watchful waiting vs. surgery

### Large Bowel Obstruction
- Pseudo-obstruction (aka Ogilvie’s)
  - Autonomic imbalance due to various causes; may result in complications like ischemia or perforation
- True obstruction
  - Medical emergency due to cancer (~60%) and diverticulum (~20%) in which complications are eminent or present
- Treatment
  - Usually watchful waiting for pseudo-obstruction and surgery for true obstruction

### Ileus Pathophysiology
- Likely multifactorial due to alteration of the normal control systems
  - Neuronal (e.g., increased sympathetic activity)
  - Hormonal (e.g., VIP)
  - Mechanical (e.g., bowel manipulation if surgery)
  - Immunomodulation (e.g., stress response with release of various cytokines)
  - Pharmacologic (e.g., exogenous opioids that alter some of the control systems listed above)

### Ileus: Causes
- Any major stressful event or a variety of factors that affect intestinal regulation
  - Surgery, trauma, severe infections, burns, myocardial infarction
  - Fluid, hormonal, and metabolic derangements
  - Intestinal inflammation or injury
  - Medications, particularly opioids
- Three major non-drug factors associated with postoperative ileus
  - Large incisions
  - Degree of physical manipulation of bowel
  - Exposure of peritonium to irritants, such as blood

### Postoperative Ileus (POI)
- Ileus expected after surgery, particularly abdominal or pelvic surgery
- Some use “adynamic” or “paralytic” to refer to a more prolonged ileus (e.g., 3 days)
- Prevalence depends on definition
  - For drug studies, ileus assumed to follow partial bowel resection and hysterectomy (number of cases/year ≈ 1 million)
- Definition of bowel recovery is tricky

### POI: Signs, Symptoms, and Diagnosis
- Not all patients have signs and symptoms
  - Anorexia, nausea (less commonly vomiting), pain, and cramping may occur
  - Typically no flatus or bowel movements
- No single diagnostic test rules in or out
  - Absence of bowel sounds not necessarily indicative of ileus
  - Scans and contrast studies mostly useful for ruling out obstruction and other complications
Resolution of POI

- Should have resolution of signs and symptoms if present during ileus
- No single diagnostic test for resolution
- Time withholding liquids or food after abdominal surgeries varies among surgeons (little evidence to substantiate prolonged delays)
- No substitute for a trial of oral or enteral feedings with potential risk for vomiting
  - May not see intolerance within hours in form of vomiting; may see as abdominal distention or lack of bowel movements over time

Economic Consequences: Hospital Discharge Data, 1980-1993\(^1,2\)

- 22 million surgical procedures annually
- 2.7 million procedures lead to POI (> 1 day)
- 750,000 patients discharged 1 day earlier (with effective management of POI)
- Potential savings of $1.1 billion/year

- Others suggest increase in length of stay (LOS) of 2-3 days, incremental costs of ~ $4100-$8800 per hospitalization\(^3-5\)

Herbal Products: Middle Ages

- Alternative medicine was in by public (physicians and classic medicine out)
- Example
  - Soporific sponge: opium, henbane, and various seeds, berries, and juices, including hemlock
  - Concoction boiled then dried
  - Sponge dipped in hot water
  - Put under nose
  - Vinegar used to awaken

Opium

- Word opion (opium) in 1st century A.D.
- Used in various oral, rectal, inhaled, and topical forms
- Poppy head on coin 2nd century A.D.
Medications: 19th Century
- Pharmaceutical industry in U.S. (Tilden & Company, and Parke, Davis and company)
- Morphine isolated by Sertturner in 1803
- Experiments begin with anesthetic agents including NO and ether
- Syringe developed in 1850s

Opioid Receptors
- Opioids continue as key agents for severe pain
- G-protein–linked receptor superfamily
- Receptor subtypes
  - $\mu$ ($\mu_1$, $\mu_2$)
  - $\delta$ ($\delta_1$, $\delta_2$)
  - $\kappa$ ($\kappa_1$, $\kappa_2$, $\kappa_3$)
- Several subtypes have been cloned, and related receptors with ligands have been identified, allowing for research at molecular and pharmacologic levels

Opioid Receptors
- Peripheral, spinal, and supraspinal opioid receptors exist
  - Relative contributions to pharmacologic effects still being investigated
- Centrally, $\mu$-opioid receptors are located in the spinal dorsal horns, periaqueductal gray matter, cerebral cortex, and other locations mainly postsynaptically
- Peripherally, $\mu$-opioid receptor activation (myenteric/submucosal plexuses, lymphocytes) inhibits GI motility and secretion

Ileus: Case Report
- 63-year-old man s/p bowel resection has been receiving morphine 4 mg/hr for three days by PCA
- Began on PCA morphine one week ago with 2 mg i.v. bolus with 10-minute lock-out interval
- Patient began oral feedings today
- M.D. wants to convert patient to oral medications and discharge tomorrow
  - Examples of wrong answers without more information
    - Acetaminophen as needed
    - Sustained-release morphine
    - Opioid without bowel regimen

End of Presentation
- You have reached the end of this presentation.
- Please select another presentation from the left menu.
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SELECTED REFERENCES


Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists


Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

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Robert MacLaren, Pharm.D., is Associate Professor in the Department of Clinical Pharmacy at the University of Colorado Denver School of Pharmacy in Aurora, Colorado. In addition, he is a clinical pharmacist in the medical intensive care unit at the University of Colorado Hospital, which is also located on the Anschutz Medical Campus in Aurora. Dr. MacLaren also serves as co-director of the critical care residency at the University of Colorado.

After completing his undergraduate degree in pharmacy at the University of British Columbia in Vancouver, Canada, Dr. MacLaren earned his Doctor of Pharmacy degree at the University of Utah in Salt Lake City and completed a critical care specialty residency in Memphis at the University of Tennessee and Baptist Memorial Hospital. He worked for two years as a critical care specialist at the Queen Elizabeth II Health Sciences Centre in Halifax, Canada, before joining the faculty at the University of Colorado.

Dr. MacLaren is a fellow of the American College of Clinical Pharmacy and the Society of Critical Care Medicine. His clinical research interests include gastrointestinal motility dysfunction associated with critical illness and the use of intravenous glutamine as a supplement to parenteral nutrition. He conducts animal studies of acetaminophen toxicity and has been involved with outcomes research of pharmacologic therapies and the impact of pharmacists in the intensive care unit. He has authored several articles relating to the pharmacologic and nutritional therapies of critically ill patients and has been an invited speaker at national and international meetings.
Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

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PRESENTATION

Managing Postoperative Ileus

ABSTRACT

In the past, the mainstay of preventing and treating postoperative ileus (POI) involved nasogastric decompression and bowel rest. However, novel approaches contradict these methods and include rapid nasogastric extubation and early feeding. Other therapies shown to be effective include the use of less invasive surgical techniques, such as laparoscopy; minimization of systemic opioid administration; epidural anesthesia/analgesia; and sham feeding. This presentation will illustrate the clinical application of these proven therapies and will also include a brief review of unproven therapies, such as prokinetic agents, early mobilization, preoperative hydration, and sympathetic suppression.

While no single therapy can eliminate POI, the combined application of these modalities is effective. An interdisciplinary concept to accelerate postoperative convalescence and reduce general morbidity by simultaneously applying several interventions is termed multimodal care and produces a fast-track treatment approach. This presentation will develop strategies for implementing multimodal, fast-track care with an emphasis on involving the pharmacist.

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to

- Describe the rationale and clinical outcomes for at least three components included in the multimodal approach of preventing and treating postoperative ileus.
- Describe the role of the health-system pharmacist in preventing and managing postoperative ileus.
- Given pertinent patient information, recommend strategies for preventing and treating postoperative ileus.
Managing Postoperative Ileus

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Learning Objectives

• Describe the rationale and clinical outcomes for the components included in the multimodal approach of preventing and treating postoperative ileus (POI)
• Describe the role of the health-system pharmacist in preventing and managing POI
• Given pertinent patient information, recommend strategies for preventing and treating POI

Ileus: Case Revisited
• 63-year-old man s/p bowel resection has been receiving morphine 4 mg/hr for three days by patient-controlled analgesia (PCA)
• Began PCA morphine one week ago with 2-mg i.v. bolus with 10-minute lock-out interval
• Patient just started oral feedings today
• M.D. wants to convert patient to oral medications and discharge tomorrow

Prevention and Management of POI

Preoperative measures
• Hydration and premedication
  – Surgical techniques
  – Anesthetic choice and route
  – Opioid-sparing analgesics
  – Mobilization (ambulation)
  – Others
    • Sham feeding
    • Hyperbaric oxygen
    • Electrical stimulation, psychological suggestion, mechanical message, acupuncture, herbals
  • Avoid medications that reduce gastrointestinal (GI) motility

Postoperative measures
• Opioid route
• Early oral or enteral feeding
• Fluid management
• Prokinetic agents, laxatives, neostigmine

“Multimodal Care” = “Fast-Track” Recovery

POI (the role of the pharmacist)

Laparoscopic surgery
NG tube removal
Opioid sparing
Laxatives, prokinetics
Sympathetic anesthetics
Mobilization?
Early feeding, fluid management

What is “Fast-Track Recovery”?• “An interdisciplinary multimodal concept to accelerate postoperative convalescence and reduce general morbidity (including POI) by simultaneously applying several interventions.”

Preoperative Measures
• Hydration
  – Preoperative administration of glucose containing fluids reduces postoperative insulin resistance and catabolic response BUT keeps normoglycemia
• Premedication
  – Anxiolytic agents (benzodiazepines) reduce sympathetic-related complications and catabolic response
  – Clonidine and β-blockers reduce intraoperative hemodynamic fluctuations AND have analgesia-sparing properties while optimizing analgesia
  – R, DB study of 29 colorectal cases showed propranolol 4 mg i.v. every 12 hr starting 30 min before surgery reduced time to first bowel movement (82 ± 11 vs. 110 ± 9 hr, p < 0.01)

R, DB= randomized, double blind

Intraoperative Measures: Laparoscopic Surgery

- Meta analysis of 22 trials \((n=2965)\) of colorectal surgery
  - Reduced blood loss of 71.8 mL \((95\% \text{ CI}, 30.8-113 \text{ mL}; p=0.0006)\)
  - Reduced postoperative pain by 9.3/100 (95\% CI, 5.4-13.2; \(p<0.0001\))
  - Earlier flatulence by 1 day (95\% CI, 0.76-1.3; \(p<0.0001\))
  - Earlier bowel movement by 0.9 days (95\% CI, 0.74-1.13; \(p<0.0001\))
  - Lessened ileus \(\text{RR}=0.40 \text{ 95\% CI, 0.22-0.73; } p=0.003\))
  - Reduced wound infections \(\text{RR}=0.56 \text{ 95\% CI, 0.39-0.89; } p=0.002\))
  - Shortened hospital length of stay \(\text{LOS})\) by 1.5 days (95\% CI, 1.12-1.94; \(p<0.0001\))


Intraoperative Measures: Laparoscopic Surgery (cont)

- Another meta analysis of 49 trials \((n=6438)\) of colorectal surgery
  - Reduced pain and opioid requirements by 16-35%
  - Earlier flatulence, bowel movement, or tolerating diet by 1.2-1.6 days (26-37% shorter)
  - Shortened LOS by 3.5 days (18.8%)


Why Would Laparoscopic Surgery Improve Outcomes?

- Smaller incisions
- Less handling of intestine (particularly the colon) and less inflammation
- Less pain = less opioid used
- Earlier ambulation
- Less exposure to air and endotoxin
- Improved immune consequences
- Fewer NG tubes and earlier diet

Intraoperative Measures: Surgical Techniques

- Level of surgical training impacts GI motility
  - Multivariate regression analysis of 124 colorectal surgeries
  - Factors contributing to delayed flatulence was lack of fellowship training \((\text{OR}=3.32; p=0.001)\)
  - Factors contributing to delayed bowel movements
    - Lack of fellowship training \((\text{OR}=3.13; p=0.002)\)
    - Systemic opioids \((\text{OR}=2.62; p=0.01)\)


Anesthetic Choice and Route

- Almost all intraoperative inhaled or i.v. anesthetics temporarily inhibit GI motility
  - Level of monitoring is important!
- Epidural anesthesia/analgesia synergistically block inhibitory sympathetic reflexes, prevent the release of afferent pain neurotransmitters, and increase splanchnic blood flow
- Epidural anesthetics dose-dependently block nociceptive and autonomic fibers first and motor and somatosensory fibers last
- Epidural analgesia reduces opioid adverse effects
- Use of local anesthesia and nerve blocks further reduce systemic exposure


Postoperative Measures
Epidural vs. PCA Administration of Opioids

<table>
<thead>
<tr>
<th>At rest</th>
<th>On mobilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileus</td>
<td>++</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>++</td>
</tr>
<tr>
<td>Sedation</td>
<td>++</td>
</tr>
<tr>
<td>Hypotension</td>
<td>+/-</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>+/-</td>
</tr>
<tr>
<td>Workload</td>
<td>++</td>
</tr>
</tbody>
</table>

Epidural vs. PCA Administration of Opioids (cont)

- BUT... Studies consistently show
  - Epidural anesthesia/analgesia at T8-10 is more effective than PCA for analgesia with fewer adverse effects
  - Morphine is hydrophilic and may reduce epidural-associated adverse events (except pruritus)
- AND... Epidural anesthesia reduces time to GI recovery
  - By 37 hr (19-56) compared with systemic opioids
  - By 24 hr (10-39) compared with epidural opioids
  - But, analgesia better by 20/100 (8.4-31.5) with epidural anesthesia/analgesia

Epidural vs. Parenteral

- Meta analysis of 16 trials (n=806) of colorectal surgery
  - **Reduced postop pain** by 15-18/100 (95% CI, 10-26; p<0.001)
  - **Earlier bowel function** by 1.6 days (95% CI, 0.84-2.3; p<0.001)
  - Also saw...
    - Increased hypotension (OR=13.5 95% CI, 4-57.7; p<0.001)
    - Pruritus (OR=4.8 95% CI, 1.3-17; p=0.02)
    - Urinary retention (OR=4.3 95% CI, 1.2-15.9; p=0.03)

NG Tubes

- NG tubes routinely inserted for gastric decompression until return of bowel function
- Early removal of NG intubation
  - Meta analysis of 28 trials (n=4194) of abdominal surgery
    - **Accelerated bowel recovery** by 0.52 days (95% CI, 0.46-0.57; p=0.0001)
    - **Earlier flatulence** by 0.53 days (95% CI, 0.28-0.78; p=0.0004)
    - **Reduced vomiting** (OR=0.66 95% CI, 0.45-0.95; p=0.03)
    - **Reduced pulmonary complications** (RR=1.45 95% CI, 1.08-1.92; p=0.01)
    - **Shortened LOS** by 1.21 days (95% CI, 0.56-1.86; p<0.0001)

Early Oral or Enteral Feeding

- Convention is restriction of enteral intake
- Early oral or enteral feeding (within 24 hours)
  - Meta analysis of 13 trials (n=1173) of colorectal surgery
    - **Less vomiting** (RR=1.27 95% CI, 1.01-1.61; p=0.04)
    - Shortened LOS by 0.89 days (95% CI, 0.20-1.58; p=0.01)
    - Reduced mortality (RR=0.41 95% CI, 0.18-0.93; p=0.03)
  - Meta analysis of three trials (n=413) of abdominal gynecologic surgery
    - **Reduced nausea** (RR=1.79 95% CI, 1.19-2.71; p=0.006)
    - **Earlier bowel sounds** by 0.50 days (95% CI, 0.16-0.84)
    - **Shortened time to intake of solid food** by 1.47 days (95% CI, 0.69-2.26; p=0.0004)
    - **Shortened LOS** by 0.73 days (95% CI, 0.07-1.52; p=0.07)

Rationale

- Why would NG tube removal improve outcomes?
  - Resumption of oral intake
- Why would early oral or enteral feeding improve outcomes?
  - Counteracts catabolism
  - Improves immune function
  - Hastens wound healing
Fluid Management

- 20 patients with colonic resection randomized to receive postoperative daily intake of ≥3L water and 154 mEq sodium vs. ≤2L and 77 mEq sodium for 4-5 days

<table>
<thead>
<tr>
<th>Standard</th>
<th>Restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net estimated water balance L over 5 days</td>
<td>3.7 (2.4-5.8)</td>
</tr>
<tr>
<td>Passing flatulence, days 4 (4-5)</td>
<td>3 (2-3)*</td>
</tr>
<tr>
<td>Bowel movement, days 6.5 (5.8-8)</td>
<td>4 (3-4)*</td>
</tr>
<tr>
<td>Enteral intake, days 6.5 (5.5-7)</td>
<td>4 (4-4.3)*</td>
</tr>
<tr>
<td>Adverse events, n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Hospital LOS, days 9 (7.8-14.3)</td>
<td>6 (5-7)*</td>
</tr>
</tbody>
</table>

Goal: Euvolemia without dehydration and electrolyte abnormalities

Opioid-Sparing Analgesia

- 40 colectomy patients
  - Correlation between morphine PCA dose and first bowel sounds ($p=0.001$), flatulence, ($p=0.003$), and first bowel movement (shown, $p=0.002$)
  - No correlation between incision length and morphine dose
  - ICD-9-CM coded POI correlates with systemic morphine (OR=12.1; 95% CI, 5.4-27.1)

Opioid-Sparing Analgesia (cont)

- Surveys indicate patients prefer inadequate pain relief over adequate analgesia with associated bowel dysfunction

Mobilization (Ambulation)

- Important for preventing postoperative thrombi and pneumonia
- Thought to increase gastrointestinal blood flow to enhance motility
  - Gastrointestinal electrical recording of 34 laparotomy cases (ambulation day 1 vs. day 4) showed no differences in myoelectrical activity along any segment
- Fast-track programs incorporating early mobilization show mixed results

Prokinetic Agents

- Metoclopramide improves nausea but...

---

Laxatives and Neostigmine

- Only one randomized study of 20 colectomy cases of bisacodyl vs. placebo suppositories
  - By postoperative day (POD) 3, all patients taking bisacodyl defecated vs. 3 patients taking placebo ($p<0.001$)
  - LOS: $8.5 \pm 2.7$ vs. $10.4 \pm 5.3$ days
- Neostigmine not studied and too many adverse events


Sham Feeding

- Meta analysis of 5 trials ($n=158$) of colorectal surgery
  - Earlier flatulence by 20.8 hours (95% CI, 8.9-32.6; $p=0.0006$)
  - Earlier bowel movement by 33.3 hours (95% CI, 15.7-50.8; $p=0.0002$)
  - Shortened LOS by 2.44 days (95% CI, 1.77-3.1; $p=0.0001$)
  - Fewer complications (OR=0.45 95% CI, 0.2-1; $p=0.05$)
- Why would sham feeding improve outcomes?
  - Stimulation of the vagal reflex to enhance cholinergic motility
  - Secretion of GI hormones and enzymes


Other Postoperative Measures

- Hyperbaric oxygen therapy may prevent and treat POI (case series)
- Electrical stimulation via intermittent transcutaneous “pacing” or electromagnetic energy
  - Earlier return of bowel sounds but not function (case series and small studies)
- Randomized study of light massage of the abdominal wall after colectomy in 50 patients
  - Earlier flatulence (1.8 vs. 3.6 days, $p<0.01$)
  - Lower pain scores and opioid use


Other Postoperative Measures (cont)

- Randomized study of acupuncture restored normal bowel function within 72 hours of colectomy in 12/13 vs. 6/13 patients ($p=0.009$)
- Randomized study of Dai-kenchu-to and Keish-bukuryo-gan after colectomy in 66 patients
  - Earlier flatulence and tolerance of diet
  - Shortened hospital LOS


Summary:

Therapies with Proven Benefit

- Laparoscopic surgery
- Epidural anesthesia/analgesia at T8-10
- NG tube removal
- Early oral or enteral feeding while maintaining euvolemia
- Minimization of opioid administration (opioid-sparing)
- Sham feeding

Summary:

Therapies with NO Proven Benefit

- Early mobilization
- Prokinetic agents
Summary: Therapies Yet to be Proven
- Preoperative hydration and pharmacologic therapies
- Level of surgical training
- Laxatives
- Others
  - Hyperbaric oxygen
  - Electrical stimulation
  - Light abdominal massage
  - Acupuncture
  - Herbal agents

Ileus: Case Revisited
- What could have been done differently?
  - Preoperative care and education
  - Epidural anesthesia/analgesia
  - Minimize opioids (rather than escalating)
  - NG tube removal
  - Laxative
  - Early oral or enteral feeding
  - Sham feeding if oral feeding not possible
- How could the process improve to ensure efficiency?
  - Multimodal, fast-track care

Multimodal Components: Preoperative Components
- Provide patient education
- Stabilize coexisting diseases
- Optimize comfort (minimize anxiety)
- Ensure hydration, normalized electrolytes, normoglycemia, and normothermia
- Ensure appropriate use of prophylactic therapy (nausea, ileus, pain, antibiotic)

Multimodal Components: Intraoperative Components
- Anesthesia to optimize surgery and recovery
- Local anesthesia/analgesia (or thoracic epidural) if possible
- Laparoscopic surgery if possible (gentle handling of tissue)

Multimodal Components: Postoperative Components
- Remove NG tube
- Laxative, start oral feedings early (vs. sham feedings)
- Minimize opioids
- Ambulate
- Discharge criteria

Fast-Track Example (Colectomy)

Multimodal Outcomes

- Expedited gastrointestinal recovery
- Earlier oral nutrition
- Fewer complications
- Shortened hospital LOS
- Fewer re-admissions
- Cost minimization
- Greater patient satisfaction?
- Best results with epidural anesthesia/analgesia

Role of the Pharmacist

- Medication protocol
  - Comfort (minimize anxiety)
  - Appropriate hydration, normalized electrolytes, normoglycemia, and normothermia
  - Appropriate use of prophylactic therapy (nausea, ileus, pain, antibiotic)
  - Postoperative analgesia (with opioid minimization) and pain assessment
  - Laxatives

Role of the Pharmacist (cont)

- Stabilize coexisting diseases
- Advocate diet
- Promote mobilization
- Team member and education of team
- Discharge planning
- Patient education and compliance assessment

The Future

- Identification of risk factors for POI
- Patient-centered care
  - Hydration and electrolytes
  - Opioid regimen and opioid-sparing therapies
  - Anxiolytic and anti-emetic therapies
- Pharmacologic modification of the "stress response"
- Multidisciplinary PACUs
- Clinical pathways
- Outreach services for rehabilitation
- Hyperbaric oxygen therapy, electrical stimulation, acupuncture
- New agents: peripherally active selective opioid antagonists (methylnaltrexone, alvimopan), motilin agonists (atilmotin)

Time to Change the Way We Think About POI!

- Classic view: Postoperative ileus is an inevitable response to major surgery that prolongs hospitalization and causes significantly diminished patient quality of life
- New view: Pharmacists can participate in the proactive prevention and treatment of postoperative ileus to help facilitate hospital discharge, lower hospitalization costs, and improve patient outcomes

End of Presentation

- You have reached the end of this presentation.
- Please select another presentation from the left menu.
Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

SELECTED REFERENCES


Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists


Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

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Clinical Coordinator
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Michael D. Kraft, Pharm.D., is Clinical Assistant Professor at the University of Michigan College of Pharmacy in Ann Arbor, Michigan. His practice site is at the University of Michigan Health-System, where he serves as Clinical Coordinator and Clinical Pharmacist in Surgery and Nutrition. He earned his Doctor of Pharmacy degree from the University of Michigan College of Pharmacy, and then completed a specialty residency in critical care and nutrition support at the University of Tennessee at Memphis before returning to his alma mater as a faculty member.

At the college, Dr. Kraft teaches several topics, including fluids and electrolyte pathophysiology, acid-base pathophysiology, and parenteral nutrition support. His research interests include nutrition support, drug-nutrient interactions, infectious diseases in surgical and critically ill patients, drug and nutrition therapy during continuous renal replacement therapy, adverse drug events, gastrointestinal dysfunction in critically ill patients, and postoperative ileus. He has authored several articles and book chapters, and his writings have appeared in Pharmacotherapy, American Journal of Health-System Pharmacy, Nutrition in Clinical Practice, Journal of Pediatric Pharmacology and Therapeutics, and Chemical Research in Toxicology. He regularly makes presentations at local, regional, and national conferences on postoperative ileus, perioperative nutrition support, nutrition support in critically ill patients, sepsis, treatment of nosocomial pneumonia, and appropriate empiric antibiotic therapy and antibiotic resistance.

Dr. Kraft is an active member of several professional associations, including the American Society of Health-System Pharmacists, American Society for Parenteral and Enteral Nutrition (ASPEN), Michigan Society for Parenteral and Enteral Nutrition (MSPEN), American College of Clinical Pharmacy (ACCP), Society of Critical Care Medicine (SCCM), and Michigan Pharmacists Association (MPA). He currently serves as the President of MSPEN, Secretary/Treasurer of the Pharmacy Practice Section of ASPEN, and member of the Professional Affairs Committee of MPA.
Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists

Michael D. Kraft, Pharm.D.

PRESENTATION

New and Emerging Options for Managing Postoperative Ileus: Clinical Research and Potential Implications for Pharmacists

ABSTRACT

The ideal drug therapy for treating postoperative ileus (POI) would selectively antagonize the inhibitory effects on the gastrointestinal (GI) tract of all of the potential factors implicated in the pathophysiology of POI. The most promising target to date is inhibition of the \( \mu \)-opioid receptors in the GI tract and the adverse GI effects of endogenous and exogenous opioids. Opioid analgesics are an important part of the postoperative care of surgical patients, and endogenous opioids are released as part of the stress response, especially after abdominal surgery. Selective inhibition of \( \mu \)-opioid receptors in the GI tract—without reversing centrally-mediated opioid-induced analgesia—may be beneficial in reducing POI.

The nonselective opioid antagonists naloxone and nalmefene may cross the blood-brain barrier and reverse analgesic effects of opioids and, therefore, are not appropriate for preventing or treating POI. They have not been evaluated in any prospective, randomized studies for POI. The peripherally-selective opioid antagonist methylnaltrexone may shorten the duration of POI and the length of hospital stay based on results from a phase 2 study. Phase 3 studies with methylnaltrexone are ongoing. Alvimopan is a more extensively studied peripherally-selective opioid antagonist, and several phase 3 studies have shown that it reduces the duration of POI, incidence of postoperative nausea and vomiting, and length of hospital stay compared with placebo. Preliminary results of a long-term alvimopan safety study, however, revealed some potential safety concerns, including adverse cardiovascular events. The significance of these adverse events must be understood before determining the most appropriate role of alvimopan in patient care.

Should these new agents receive FDA approval, criteria for their optimal use will need to be developed. These therapies will need to be incorporated into preoperative and postoperative policies, procedures, and protocols; initiatives, such as restricting prescribing to certain prescribers or to types of patients or surgeries or both, may be appropriate. Other considerations in the formulary review process will be the safety profile of the agents and the potential cost savings if reduced patient length of hospital stay can be realized.

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to

- Describe the potential role of methylnaltrexone and alvimopan in reducing postoperative ileus and the potential impact on clinical outcomes.
- List and discuss issues that pharmacists must consider when evaluating formulary status of new drug therapies for postoperative ileus.
New and Emerging Options for Managing Postoperative Ileus:
Clinical Research and Potential Implications for Pharmacists

Michael D. Kraft, Pharm.D.
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University of Michigan College of Pharmacy
Ann Arbor, Michigan

The “Ideal” Anti-Postoperative Ileus (POI) Drug

- Selective for inhibitory mediators on gastrointestinal (GI) tract
  - Opioid inhibition appears most promising
  - Lack of central nervous system (CNS) penetration
- Easy to administer
- Well-tolerated; limited or no adverse effects

The “Ideal” Anti-POI Drug (cont)

- Available in oral and parenteral forms
- Limited systemic absorption when given by mouth (p.o.)
- No drug or disease interactions
- Inexpensive

Agents Studied

- Nonselective compounds (tertiary opioid antagonists)
  - Naloxone
  - Nalmefene
- Selective compounds (quaternary opioid antagonists)
  - Methylnaltrexone (MNTX)
  - Alvimopan

Naloxone*

- Naloxone effectively reverses effects of opioids
- Naloxone readily crosses the blood brain barrier (BBB)
  - Reversal of opioid-mediated analgesia
  - May produce withdrawal
- Dose required to reverse opioid effects is patient-specific, highly variable
- Study by Liu and Wittbrodt
  - Nine patients with chronic opioid-induced constipation
    - Naloxone 2 mg, 4 mg, or placebo 3 times daily for 3 weeks
    - All patients experienced improved bowel frequency
    - 3/9 had reversal of analgesia (1 total), several days to return to baseline

Nalmefene*

- Not selective for peripheral (gut) opioid receptors
- Nalmefene glucuronide shows selectivity in rodents
- Study by Cheskin et al.
  - Ascending doses of nalmefene glucuronide given to 5 patients maintained on chronic oral methadone
  - Drug stopped when either laxation or withdrawal occurred
  - Withdrawal symptoms observed in all 5 patients
  - Possibly due to biotransformation of glucuronide form back to the parent compound

*Not FDA approved for POI

Peripherally Selective μ-Opioid Receptor Antagonists

Methylnaltrexone*

Alvimopan*

*Investigational agents, not FDA approved

Methylnaltrexone: A Novel, Quaternary μ-Opioid Receptor Antagonist

- Addition of methyl group to naltrexone, a naloxone-derived tertiary antagonist

Methylnaltrexone (MOA-728)

- Poorly lipid soluble, does not penetrate the BBB
- Pharmacokinetics
  - Limited oral absorption, half-life ~ 2 – 4 hr (p.o. and i.v.)
    - ~ 30 – 50% recovered in urine after i.v.
    - ~ <1% recovered in urine after oral
  - Steady-state: no accumulation, minimal change in pharmacokinetics
  - Not demethylated to substantial extent in humans

Methylnaltrexone (MOA-728) (cont)

- Reverses opioid-induced slowing of gut transit time
- Does not antagonize the central (analgesic) effects of opioids or precipitate withdrawal
- Reported to be well-tolerated, no significant adverse effects
  - Diarrhea, mild-moderate abdominal cramping

Methylnaltrexone: Three Dosage Forms Being Evaluated

- Intravenous and subcutaneous
  - Completed two phase 3 trials (subcutaneously) for opioid-induced bowel dysfunction (OBD)
  - Completed a phase 2 trial (i.v.) for POI
- Oral
  - Completed two phase 1 studies in healthy volunteers (uncoated and enteric-coated)
  - Will initiate two phase 2 trials soon
Methylnaltrexone: MNTX 203 Methods

• Phase 2 study for reduction of postoperative bowel dysfunction
• Randomized, double-blind, placebo-controlled
• 65 patients undergoing segmental colectomy
• MNTX 0.3 mg/kg or placebo i.v.
  – First dose within 90 min of end of surgery, then every 6 hr
  – Up to 24 hr after GI recovery, max of 7 days
• GI recovery: tolerated solid food plus bowel movement (BM)


Methylnaltrexone: MNTX 203 Results

Reported as mean time (hr) ± S.E.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MNTX (n=33)</th>
<th>Placebo (n=32)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full liquids</td>
<td>70 ± 9</td>
<td>100 ± 19</td>
<td>0.05</td>
</tr>
<tr>
<td>1st BM</td>
<td>97 ± 6</td>
<td>120 ± 10</td>
<td>0.01</td>
</tr>
<tr>
<td>GI recovery</td>
<td>124 ± 9</td>
<td>151 ± 16</td>
<td>0.06</td>
</tr>
<tr>
<td>Discharge eligible</td>
<td>119 ± 7</td>
<td>149 ± 17</td>
<td>0.03</td>
</tr>
<tr>
<td>Actual discharge</td>
<td>140 ± 6</td>
<td>165 ± 16</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*1-sided


Clinical Trials of Methylnaltrexone

• MNTX 203: Phase 2 trial, MNTX i.v. in the prevention of postoperative ileus
• Three ongoing Phase 3 trials, MNTX i.v. for reduction of POI
  – MNTX 3301, 3200L2-300: open laparotomy and segmental colectomy
  – 3200L2-301: ventral hernia repair
  – Primary outcome: time between end of surgery and first BM

U.S. NLM. ClinicalTrials.gov (URL in reference list);
Wyeth. Clinical trial listings (URL in reference list);
Progenics Pharmaceuticals. Postoperative (IV) (URL in reference list).

Alvimopan

Alvimopan: A Novel, Quaternary μ-Opioid Receptor Antagonist

Moderately large molecular weight (461 Da)

Alvimopan

• Unique pharmacologic profile
  – Limited oral bioavailability (dogs ~ 0.03%, humans ~ 6%)
  – Majority excreted in the feces, minimal renal excretion after oral dosing (~ 0.4%)
  – Similar in elderly
• High binding affinity for μ-opioid receptor
  – K_i<1 nmol/L
  – 10-100 times less affinity for delta (δ) and kappa (κ) opioid receptors

Alvimopan (cont)
• Does not reverse opioid analgesia
• Reduces oral-cecal transit time
• Reverses morphine-induced constipation
• Data for efficacy in reducing opioid-induced bowel dysfunction
• Data for efficacy in reducing the duration of POI after bowel resection


Alvimopan for POI: Phase 3 Trials*

<table>
<thead>
<tr>
<th>Study</th>
<th>Total and MITT (n)</th>
<th>Population (% MITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14CL 302</td>
<td>Total = 451</td>
<td>Colon resection (68%)</td>
</tr>
<tr>
<td></td>
<td>MITT = 424</td>
<td>Radical hysterectomy (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simple hysterectomy (22%)</td>
</tr>
<tr>
<td>14CL 308</td>
<td>Total = 666</td>
<td>Large/small bowel resection (68%)</td>
</tr>
<tr>
<td></td>
<td>MITT = 510</td>
<td>Radical hysterectomy (17.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simple hysterectomy (14.6%)</td>
</tr>
<tr>
<td>14CL 313</td>
<td>Total = 510</td>
<td>Large/small bowel resection (96%)</td>
</tr>
<tr>
<td></td>
<td>MITT = 469</td>
<td>Radical hysterectomy (4%)</td>
</tr>
<tr>
<td>14CL 306</td>
<td>Total = 519</td>
<td>Simple hysterectomy</td>
</tr>
<tr>
<td></td>
<td>MITT = 510</td>
<td></td>
</tr>
</tbody>
</table>

*Multicenter, prospective, randomized, double-blind, placebo-controlled trials; patients underwent open laparotomy/open surgical procedure

MITT = modified intent-to-treat


Alvimopan for POI: Phase 3 Trials
• Men and women, ≥ 18 years old
• Standardized postoperative care
  – Analgesia via opioid patient-controlled analgesia (PCA)
  – Nasogastric (NG) tube out at end of surgery
  – Liquids offered, ambulation encouraged on POD 1
  – Solid food offered on POD 2
• Exclusions: Opioids within 1-4 weeks, epidural opioids, local anesthetics, nonsteroidal antiinflammatory drugs (NSAIDs), or severe concomitant disease(s)


Other Variables of Interest
• Visual analogue scale (VAS) pain scores
• Daily postoperative opioid consumption
• Incidence of NG tube insertion after surgery
• Safety


Alvimopan Study 14CL 313
Alvimopan 14CL 313: Patient Demographics (MITT)


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo 149</th>
<th>Alvimopan 6 mg (n = 155)</th>
<th>Alvimopan 12 mg (n = 165)</th>
<th>Total n = 469</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) age, yr</td>
<td>60.9 (20-87)</td>
<td>59.3 (19-89)</td>
<td>61.3 (20-89)</td>
<td>60.5 (19-89)</td>
</tr>
<tr>
<td>Mean (median) surgery duration, hr</td>
<td>2.2 (1.9)</td>
<td>2.1 (1.9)</td>
<td>2.1 (1.9)</td>
<td>2.1 (1.9)</td>
</tr>
<tr>
<td>Intraoperative opioid use, mg</td>
<td>26.5</td>
<td>28.1</td>
<td>25.5</td>
<td>--</td>
</tr>
<tr>
<td>Postoperative opioid use, mg</td>
<td>27</td>
<td>33.6*</td>
<td>27.1</td>
<td>--</td>
</tr>
</tbody>
</table>

*Significantly higher vs. placebo and 12 mg

Alvimopan 14CL 313: Results


<table>
<thead>
<tr>
<th>Endpoint/Treatment</th>
<th>Placebo</th>
<th>Alvimopan 6 mg</th>
<th>Alvimopan 12 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, hr (Δ vs. placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First solid food + BM/flatus (GI-3)</td>
<td>26 (17.4)</td>
<td>16 (10.3)</td>
<td>16 (9.7)</td>
<td>120</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Alvimopan 6 mg</td>
<td>1.28 (1.0-1.64)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Alvimopan 12 mg</td>
<td>1.54 (1.21-1.96)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint/Treatment</th>
<th>Placebo</th>
<th>Alvimopan 6 mg</th>
<th>Alvimopan 12 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, hr (Δ vs. placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First solid food + BM (GI-2)</td>
<td>39 (26.2)</td>
<td>25 (16.1)</td>
<td>25 (15.2)</td>
<td>133</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Alvimopan 6 mg</td>
<td>1.38 (1.07-1.79)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Alvimopan 12 mg</td>
<td>1.67 (1.30-2.15)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>p value</td>
<td>0.013</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</table>

Alvimopan 14CL 313: Results (cont)


<table>
<thead>
<tr>
<th>Endpoint/Treatment</th>
<th>Placebo</th>
<th>Alvimopan 6 mg</th>
<th>Alvimopan 12 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, hr (Δ vs. placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital DCO written</td>
<td>12 (12.1)</td>
<td>10 (6.5)</td>
<td>9 (5.5)</td>
<td>146</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Alvimopan 6 mg</td>
<td>1.25 (0.98-1.58)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Alvimopan 12 mg</td>
<td>1.42 (1.12-1.79)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>p value</td>
<td>0.070</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Alvimopan 14CL 313: Adverse Events


<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo n = 166</th>
<th>Alvimopan 6 mg n = 169</th>
<th>Alvimopan 12 mg n = 176</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>64.2 %</td>
<td>(60.9 %)</td>
<td>(54.5 %)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25.3</td>
<td>(24.3)</td>
<td>(19.9)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13.9</td>
<td>(13.6)</td>
<td>(13.6)</td>
</tr>
<tr>
<td>Oliguria</td>
<td>15.2</td>
<td>(11.8)</td>
<td>(13.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.9</td>
<td>(11.8)</td>
<td>(12.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13.9</td>
<td>(14.2)</td>
<td>(10.8)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>15.2</td>
<td>11.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>13.9</td>
<td>(13.0)</td>
<td>(10.8)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>17.0</td>
<td>(10.7)</td>
<td>(9.7)</td>
</tr>
</tbody>
</table>

Alvimopan 14CL 313: Morbidity


- Reduced incidence of postoperative NG tube insertion vs. placebo
  - 4.8% alvimopan 12 mg vs. 14.8% placebo; p = 0.004
- Significant reduction of “delayed” POI vs. placebo
  - 8.3% alvimopan 6 mg vs. 6.3% alvimopan 12 mg vs. 15.8% (placebo); p < 0.05
- Decreased readmission rates (within 10 days)
  - 4% alvimopan-treated patients
  - 8% placebo

Alvimopan Phase 3 Pooled Analyses

Meta-Analysis: Alvimopan vs. Placebo

- Included 5 trials, 2195 patients
  - Alvimopan = 1521, placebo = 674
  - Bowel resection ~ 56%, total abdominal hysterectomy (TAH) ~ 44%

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI-3 (alvimopan 12 mg vs. placebo)</td>
<td>1.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI-3 (alvimopan 6 mg vs. placebo)</td>
<td>1.50</td>
<td>0.003</td>
</tr>
<tr>
<td>GI-2 (alvimopan 12 mg vs. placebo)</td>
<td>1.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI-2 (alvimopan 6 mg vs. placebo)</td>
<td>1.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time ready for DC (alvimopan 12 mg)</td>
<td>1.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time ready for DC (alvimopan 6 mg)</td>
<td>1.40</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- No significant reduction in nausea, vomiting, prolonged POI, abdominal distention

DC = discharge  

Alvimopan: Pooled Analysis of Patients with Bowel Resection

- Included 3 trials, 1165 patients (MITT)
  - Alvimopan 12 mg = 397, alvimopan 6 mg = 385, placebo = 383

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI-3 (alvimopan 12 mg vs. placebo)</td>
<td>1.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI-3 (alvimopan 6 mg vs. placebo)</td>
<td>1.28</td>
<td>0.001</td>
</tr>
<tr>
<td>GI-2 (alvimopan 12 mg vs. placebo)</td>
<td>1.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI-2 (alvimopan 6 mg vs. placebo)</td>
<td>1.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to DCO written (alvimopan 12 mg)</td>
<td>1.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to DCO written (alvimopan 6 mg)</td>
<td>1.36</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Alvimopan significantly reduced nausea (12 mg), NG tube reinsertion, prolonged POI, readmit, or prolonged LOS


Alvimopan Study 14CL 314: Methods

- Phase 3 study, 654 patients scheduled for large or small bowel resection, MITT = 629
- Alvimopan 12 mg twice daily vs. placebo, first dose given 30-90 minutes before surgery
  - Primary endpoint: GI-2
  - Secondary endpoints: GI-3, time to first BM, time to ready for DC, time to DCO written, time to hospital departure


Alvimopan Study 14CL 314: Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Alvimopan (n=317)</th>
<th>Placebo (n=312)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI-2 (hr)</td>
<td>92.0</td>
<td>111.8</td>
<td>---</td>
</tr>
<tr>
<td>GI-2 hazard ratio</td>
<td>1.53 (1.29, 1.82)</td>
<td>---</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>5.2</td>
<td>6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POI-related morbidity (%)</td>
<td>6.9</td>
<td>14.4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

- Generally well tolerated
  - Nausea (placebo 66.2% vs. alvimopan 57.8%; p = 0.03)
  - Vomiting (placebo 24.6% vs. alvimopan 14.0%; p < 0.001)
  - Abdominal distention (placebo 20.3% vs. alvimopan 17.6%; p = 0.425)


Alvimopan Study 014

Safety Concerns
**Alvimopan: FDA Approvable Letter**

- Alvimopan study 014 safety concerns
  - 805 patients (alvimopan = 538, placebo = 267)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alvimopan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction (MI)</td>
<td>7 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>All cardiovascular (CV) severe adverse events (SAEs)</td>
<td>14 (2.6%)</td>
<td>3 (1.12%)</td>
</tr>
<tr>
<td>Neoplasms (benign, malignant, unspecified)</td>
<td>15 (2.8%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Serious</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

- Also an increase in fracture events alvimopan vs. placebo
- CV events in patients with established or high risk for CV disease
- 5 of 7 MIs occurred at two sites; incidence of MI not linked to duration

**Ileus: Case Report**

- 63-yr-old man s/p bowel resection has been receiving morphine 4 mg/hr for three days by patient-controlled analgesia (PCA)
- Began PCA morphine 1 week ago with 2-mg i.v. bolus with 10-minute lock-out interval
- Patient just started oral feedings today
- Physician wants to convert patient to oral medications and discharge tomorrow

**Emerging Drug Therapies for Postoperative Ileus:**

**Formulary Considerations**

If either methylnaltrexone or alvimopan receive FDA approval, in which patients would they be appropriate?

- Exploratory laparotomy with bowel resection
- Likely to receive opioids via PCA
- Other abdominal surgeries (e.g., TAH)?
- Surgeries other than exploratory or open laparotomy? Laparoscopic – seems unlikely to benefit
- Safety concerns? Patients with CV disease?
- Has your institution developed other pathways to reduce POI (e.g., multimodal or fast-track pathway)?

**When and how should the drug be administered?**

- Alvimopan: up to 30 – 90 min preoperatively
- What if a patient does not receive a preoperative dose of alvimopan? According to rats, less effective!1
- Methylaltrexone: postoperatively?
- Is this the best way to dose these agents (i.e. "prophylaxis")?
- More pharmacokinetics and pharmacodynamics data??
- Where to administer? In hospital
- Route of administration
- DOSING!! Dose for opioid-induced constipation and OBD will likely be lower than for POI

**How will these agents affect resources? How should they be used to realize the maximum benefit with the least impact on resources and budget?**

- Drug cost unknown
- Restrict to prescriber types (e.g., GI surgeons) or specific procedures or both?
- Decrease in actual LOS vs. time to DCO written?
- Can the reduced LOS be realized?
- Reduction in morbidity?
We can improve upon the “old way” of doing things!

Conclusions

• Methylnaltrexone and alvimopan are promising agents for the reduction of POI after bowel resection
• Methylnaltrexone phase 3 studies are underway, multiple dosage forms also being investigated
• Alvimopan is the most extensively studied agent for the reduction of POI
  – Decreased duration of POI
  – Reduced time to DCO written, possibly LOS
  – Must await further safety data and analysis
• These novel agents may become an important component of perioperative care

End of Presentation

• You have reached the end of this presentation
• Please return to the Program Overview to take the program post-test
• Or select another presentation from the left menu
Multimodal Approach for Managing Postoperative Ileus: 
Role of Health-System Pharmacists

REFERENCES


Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists


Multimodal Approach for Managing Postoperative Ileus: Role of Health-System Pharmacists


**Additional References**


SELF-ASSESSMENT QUESTIONS

1. In the normal gastrointestinal tract, what percent of nutrient absorption occurs in the jejunum?
   a. 20%.
   b. 40%.
   c. 70%.
   d. 90%.

2. According to Dr. Erstad, the four components of gastrointestinal control are
   a. Neuronal, hormonal, antibacterial, and immunomodulation.
   b. Neuronal, hormonal, mechanical, and immunomodulation.
   c. Hormonal, mechanical, psychological, and immunomodulation.
   d. Neuronal, hormonal, mechanical, and behavioral.

3. Which of the following terms is used to describe a non-mechanical obstruction of the gastrointestinal tract?
   a. Perforated bowel.
   b. Constipation.
   c. Strangulation.
   d. Ileus.

4. Small bowel obstruction occurring after abdominal surgery is a type of postoperative ileus.
   a. True.
   b. False.

5. Which of the following nondrug factors is associated with developing postoperative ileus?
   a. Physical manipulation of bowel.
   b. Short incisions during abdominal surgery.
   c. Enteral feedings given shortly after surgery.
   d. Laparoscopic surgery.

6. Which of the following statements best describes the diagnostic criteria for postoperative ileus?
   a. The absence of bowel sounds is almost always indicative of ileus.
   b. Patients are very ill and experience anorexia, nausea, and vomiting.
   c. There is no single diagnostic test to diagnose postoperative ileus or rule it out.
   d. Scans and contrast studies are routinely performed to differentiate postoperative ileus from small bowel obstruction and other complications.

7. Based on the reliability of indicators of restored bowel function after postoperative ileus, which of the following patients most likely has resolution of postoperative ileus?
   a. A patient with a normal CT scan of the colon.
   b. A patient with a normal ultrasound of the abdomen.
   c. A patient with bowel sounds and no abdominal pain.
   d. An asymptomatic patient on goal rate tube feedings.
8. The primary economic burden associated with postoperative ileus is prolonged hospitalization.
   a. True.
   b. False.

9. Which of the following statements best describes the “multimodal, fast-track approach” of caring for surgical patients?
   a. An interdisciplinary concept to expedite therapy of surgical patients in an effort to reduce postoperative complications.
   b. An interdisciplinary concept to accelerate postoperative convalescence and reduce general morbidity by simultaneously applying several interventions.
   c. An interdisciplinary concept to accelerate procedures in an effort to streamline care and decrease costs.
   d. An interdisciplinary concept to facilitate patient flow through the health care system after surgery.

10. Compared with conventional surgical techniques, laparoscopic colorectal surgery has been associated with reduced postoperative pain, earlier flatulence, and earlier bowel movement.
    a. True.
    b. False.

11. All of the following are positive effects of epidural anesthesia/analgesia in patients undergoing abdominal surgery except
    a. Synergistically blocks inhibitory sympathetic reflexes, prevents the release of afferent pain neurotransmitters, and increases blood flow to the gut.
    b. Provides a deep level of anesthesia associated with greater inhibition of gastrointestinal motility.
    c. Reduces adverse effects of opioids.
    d. Provides dose-dependent response in which nociceptive and autonomic fibers are blocked at lower doses and motor and somatosensory fibers are blocked at higher doses.

12. According to Dr. MacLaren, the goal of fluid management during the perioperative period is
    a. Euvolemia without dehydration and electrolyte abnormalities.
    b. Intake of less than 2 liters water daily for 4-5 days after surgery.
    c. Intake of at least 3 liters water daily for 4-5 days after surgery.
    d. Urine output of at least 2 liters daily.

13. A 68-year-old woman just underwent a partial colectomy and was transferred to the surgical intensive care unit after mechanical ventilation was removed. Epidural analgesia is being provided, and a nasogastric (NG) tube is in place. Which of the following options would be most beneficial for this patient in preventing or managing postoperative ileus?
    a. Start a laxative.
    b. Administer neostigmine.
    c. Remove the NG tube.
    d. Encourage mobilization.
Multimodal Approach for Managing Postoperative Ileus: 
Role of Health-System Pharmacists

14. All of the following have been shown to be beneficial in managing postoperative ileus except
   a. Early oral or enteral feeding.
   b. Administration of prokinetic agents like metoclopramide and erythromycin.
   c. Sham feeding.
   d. Reducing the amount of opioids administered by incorporating nonsteroidal anti-inflammatory agents in the pain regimen.

15. A multimodal approach to perioperative care can result in which of the following outcomes?
   a. Delayed oral nutrition.
   b. Shortened hospital length of stay.
   c. Delayed gastrointestinal recovery.
   d. Greater number of re-admissions.

16. All of the following are ways in which pharmacists can contribute to the multimodal, fast-track care of surgical patients except
   a. Develop medication protocols.
   b. Provide patient education and compliance assessment.
   c. Aid in discharge planning.
   d. Recommend maximum scheduled doses of opioids to minimize pain.

17. Which of the following drugs is a tertiary opioid antagonist that readily crosses the blood brain barrier?
   a. Methylnaltrexone.
   b. Naloxone.
   c. Meperidine.
   d. Alvimopan.

18. Which of the following statements best describes the results of clinical studies evaluating methylnaltrexone for postoperative ileus?
   a. It may reverse centrally-mediated opioid analgesia.
   b. It may reduce the time to first bowel movement in patients undergoing bowel resection via open laparotomy.
   c. It may accumulate in patients after multiple doses.
   d. It was associated with shortened time to bowel recovery and length of stay after open laparotomy and bowel resection in several phase 3 studies.

19. Based on available clinical studies, alvimopan and methylnaltrexone are administered only by the oral route.
   a. True.
   b. False.

20. The results of phase 3 clinical studies comparing alvimopan with placebo suggest that alvimopan is associated with all of the following outcomes following major abdominal surgery except
   a. Increased postoperative nausea and vomiting.
   b. Shortened time to bowel recovery.
   c. Reduced incidence of postoperative nasogastric tube insertion.
   d. Reduced time to discharge order written.
21. When making formulary decisions regarding new drug therapies for reducing postoperative ileus, all of the following could be potentially useful to consider except a. Limit their use to patients at least 50 years old.
   b. Limit their use to patients undergoing procedures for which phase 3 data have demonstrated potential benefit.
   c. Review all potential safety issues associated with the use of these agents.
   d. Develop a medication administration protocol, including the timing of the first dose relative to the start of surgery, as well as the most appropriate dose, route, and duration of therapy.

22. Based on the results of phase 2 studies (and pending phase 3 studies and further data and analysis on safety), which of the following patients could be the best candidate to receive methylnaltrexone?
   a. 60-year-old man 2 hours before undergoing a large bowel resection via open laparotomy.
   b. 50-year-old woman 6 days after undergoing a total abdominal hysterectomy who has not had return of bowel function (i.e. no flatus, no bowel movement, nothing by mouth).
   c. 65-year-old woman 1 hour after undergoing a large bowel resection via open laparotomy.
   d. 14-year-old girl 1 hour before undergoing a laparoscopic appendectomy.

23. Based on the results of phase 3 studies (and pending further data and analysis on safety), all of the following patients could be a candidate for receiving alvimopan except
   a. A 62-year-old woman 1 hour before undergoing a large bowel resection via open laparotomy.
   b. A 45-year-old man 3 hours before undergoing a small bowel resection via open laparotomy.
   c. A 53-year-old man 45 minutes before undergoing an exploratory (open) laparotomy and planned bowel resection for likely bowel perforation.
   d. A 38-year-old woman 4 days after a large bowel resection via open laparotomy who has not had return of bowel function (i.e. no flatus, no bowel movement, nothing by mouth).