Neostigmine for the Treatment of Acute Colonic Pseudo-Obstruction—Adult—Inpatient—Clinical Practice Guideline

Table of Contents

SCOPE ...................................................................................................................................... 5
METHODOLOGY ...................................................................................................................... 5
DEFINITIONS: ........................................................................................................................... 6
INTRODUCTION ....................................................................................................................... 6
RECOMMENDATIONS .............................................................................................................. 7
UW HEALTH IMPLEMENTATION ............................................................................................. 9
REFERENCES ......................................................................................................................... 10

Note: Active Table of Contents
Click to follow link

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Executive Summary

Guideline Overview
These clinical practice guidelines are intended to guide clinicians and provide appropriate criteria for the use of intravenous neostigmine in the treatment of acute colonic pseudo-obstruction (ACPO) or Ogilvie syndrome.

Key Practice Recommendations

1. Supportive Therapy
   1.1. Supportive therapy is indicated for all patients with ACPO (Class I, Level C)
   1.2. Supportive therapy includes nothing by mouth, nasogastric suction, rectal decompression, intravenous fluid replacement and correction of electrolyte imbalances, especially hypokalemia and hypomagnesemia.¹ (Class I, Level C)
   1.3. Avoid all drugs that can delay gut motility such as opioids, anticholinergics and calcium channel blockers. Laxatives, particularly osmotic compounds such as lactulose, are contraindicated as they may promote colonic bacterial fermentation, thereby increasing gas production.¹ (Class IIa, Level C)

2. Intravenous Neostigmine
   2.1. Intravenous neostigmine is safe and effective in the treatment of ACPO in patients who fail supportive therapy (Class I, Level A)
   2.2. Standard dose based on randomized controlled trails (RTCs): 2 mg IV over 3-5 min.²,³ (Class I, Level A)
   2.3. Administration of polyethylene glycol electrolyte – balanced solution via nasogastric tube has been shown to significantly decrease the rate of relapse of ACPO.⁴ The recommended dose of polyethylene glycol 29.5g daily.⁴ (Class I, Level B)
   2.4. A second dose of neostigmine 2 mg IV over 2 – 3 min may be considered in patients who fail to respond to the initial dose.²,⁵,⁶ (Class IIa, Level C) Although the timing of the second dose of neostigmine is not well established⁵, one RCT successfully used a second dose of neostigmine in non-responders 3 hours after the initial dose.² (Class IIa, Level B)
   2.5. Doses of 0.4 - 0.8 mg/hr. IV over 24 hours or 2 - 5 mg IV over 30 minutes have been successfully used in RTCs (Class IIb, Level B).⁷,⁸
   2.6. Oral neostigmine is not recommended because of its erratic absorption in the GI tract (1 - 2%).⁹,¹⁰ (Class III, Level C)

3. Administration of Intravenous Neostigmine and Monitoring
   3.1. Neostigmine 2 mg IV push is administered over 3 - 5 minutes.²,³ (Class I, Level A)
   3.2. Continuous presence of a physician knowledgeable in ACLS on the unit and a nurse in patient’s room for 30 minutes after dose administration is required. (Class I, Level C)
   3.3. Continuous telemetry monitoring for 30 minutes after dose administration is required to observe for bradycardia or asystole. (Class I, Level C)
   3.4. Monitor blood pressure every 15 minutes x 2 (Class I, Level C)
   3.5. Monitor respiratory rate and depth every 15 minutes x 2 (Class I, Level C)
3.6. Patient should be kept supine for 30 minutes, with a bedpan readily available (Class I, Level C)

3.7. Crash cart kept immediately outside of patient’s room (Class I, Level C)

3.8. The safety and efficacy of neostigmine injection in the treatment of ACPO has not been established in children (Class III, Level C)

3.9. The onset of action of intravenous neostigmine is 1 - 20 min, with duration of action of 1 - 2 hours. The average elimination half-life is 80 minutes, which is extended in patients with renal insufficiency.\textsuperscript{11,12}

4. Contraindications

4.1 Do not use neostigmine in the following conditions (Class III, Level C)
   4.1.1 Hypersensitivity to neostigmine
   4.1.2 Baseline heart rate < 60 bpm or systolic blood pressure < 90 mm Hg
   4.1.3 Uncontrolled arrhythmias
   4.1.4 Mechanical intestinal or urinary tract obstruction
   4.1.5 Signs of bowel perforation, ischemia, peritonitis, or acidosis
   4.1.6 Renal insufficiency
   4.1.7 Pregnancy
   4.1.8 Severe bronchospasm

Companion Documents
Not applicable

Pertinent UW Health Policies & Procedures
Not applicable

Patient Resources:
Not applicable
Scope
Disease/Condition(s):
Adult patients diagnosed with Acute Colonic Pseudo-obstruction (ACPO)

Clinical Specialty:
Gastroenterology, General Surgery, Internal Medicine

Intended Users:
Physicians, Physician Assistants, Advanced Practice Nurses, Pharmacists and Nurses

CPG objective(s):
To provide recommendations and criteria for the use of intravenous neostigmine in patients with ACPO

Target Population:
Adult inpatients with ACPO

Interventions and Practices Considered:
Use of supportive therapy and intravenous neostigmine in the management of patients with ACPO

Major Outcomes Considered:
Successful management of patients with ACPO with supportive therapy and intravenous neostigmine
Avoidance of drug toxicity when using intravenous neostigmine

Guideline Metrics:
1. Successful management of patients with ACPO with supportive therapy and intravenous neostigmine
2. Avoidance of drug toxicity when using intravenous neostigmine for ACPO
3. Medication use evaluation (MUE) will be performed 2 years after the approval of this guideline
4. Review of safety concerns related to the use of intravenous neostigmine for the treatment of ACPO as documented in the Patient Safety Network (PSN)

Methodology
Methods Used to Collect/Select the Evidence:
A literature search was performed using Medline, Cochrane, and PubMed databases, using the keywords “neostigmine”, “acute colonic pseudo-obstruction” and “Ogilvie syndrome”
Methods Used to Assess the Quality and Strength of the Evidence:
A modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology was used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline. 

Definitions:
Acute colonic pseudo-obstruction (ACPO) or Ogilvie syndrome - is characterized by massive colonic dilation in the absence of mechanical obstruction. 

Introduction
Acute colonic pseudo-obstruction is characterized by abdominal distension, pain, nausea and/or vomiting, with a failure to pass flatus and stools documented in up to 60 per cent of patients. Patients with complications present with marked abdominal tenderness and systemic features such as fever and tachycardia. 

Ischemia and perforation are serious complications of ACPO; spontaneous perforation has been reported in 3% to 15% of patients with a mortality rate of 50% or higher. The rate of perforation and/or ischemia rapidly increases with cecal diameters >10 to 12 centimeters and when the duration of distention exceeds 6 days. 

The differential diagnosis includes mechanical obstruction and toxic megacolon due to Clostridium difficile infection. The diagnosis of ACPO depends on accurate clinical
observations and radiographic evidence to differentiate mechanical obstruction from pseudo-obstruction in all situations of large bowel obstruction.\textsuperscript{1}

The pathogenesis of ACPO is not well understood. It is thought to occur as a result of an alteration in the autonomic regulation of colonic motor function.

The vast majority of patients with ACPO (> 95%) have the syndrome in association with one or more of multiple predisposing factors or clinical conditions.\textsuperscript{14} The most common causes of ACPO is associated with surgery 23\%, non-operative trauma 11\%, and cardiac disease (10 - 18\%).\textsuperscript{15,16} Other causes include neurological diseases (such as Parkinson\’s and Alzheimer\’s), severe infections (particularly those induced by Gram-negative bacteria), electrolyte imbalance/metabolic alterations (for example hypokalemia).\textsuperscript{1} ACPO can be compounded by drugs such as antidepressants, phenothiazines, antiparkinsonian agents and opioids/narcotics.\textsuperscript{1,5}

Supportive measures are indicated for all patients with ACPO even those in whom an invasive approach is immediately necessary.\textsuperscript{1} The duration of supportive therapy should not exceed 48 - 72 hours.\textsuperscript{1} A duration of 6 days has been shown to be associated with a greater risk of complications.\textsuperscript{5,17}

**Recommendations**

1. **Supportive Therapy**
   1.1. Supportive therapy is indicated for all patients with ACPO *(Class I, Level C)*. Supportive therapy includes nothing by mouth, nasogastric suction, rectal decompression, intravenous fluid replacement and correction of electrolyte imbalances, especially hypokalemia and hypomagnesaemia.\textsuperscript{1} *(Class I, Level C)*
   1.2. The duration of supportive therapy should not exceed 48-72 hours. A duration of 6 days has been shown to be associated with a greater risk of complications.\textsuperscript{1}
   1.3. Avoid all drugs that can delay gut motility such as opioids, anticholinergics and calcium channel blockers. Laxatives, particularly osmotic compounds such as lactulose, are contraindicated as they may promote colonic bacterial fermentation, thereby increasing gas production.\textsuperscript{1} *(Class IIa, Level C)*

2. **Intravenous Neostigmine**
   2.1. Intravenous neostigmine is safe and effective in the treatment of ACPO in patients who fail supportive therapy.\textsuperscript{8} *(Class I, Level A)*
   2.2. Standard dose based on randomized controlled trials (RTCs): 2 mg IV over 3-5 min.\textsuperscript{2,3} *(Class I, Level A)*
   2.3. Administration of polyethylene glycol electrolyte – balanced solution via nasogastric tube has been shown to significantly decrease the rate of relapse of ACPO.\textsuperscript{4} The recommended dose of polyethylene glycol 29.5g daily. *(Class I, Level B)*
   2.4. A second dose of neostigmine 2 mg IV over 2 – 3 min may be considered in patients who fail to respond to the initial dose.\textsuperscript{2,5,6} *(Class I, Level C)*
2.4.1. Although the timing of the second dose of neostigmine is not well established, one randomized control trial successfully used a second dose of neostigmine in non-responders 3 hours after the initial dose.\(^2,5\) \textit{(Class IIa, Level B)}

2.5. Doses of neostigmine 2 - 5 mg IV over 30 minutes may be considered.\(^7,8\) \textit{(Class IIb, Level B)}

2.6. Oral neostigmine is not recommended because of its erratic absorption in the GI tract (1 - 2\%)\(^9,10\). \textit{(Class III, Level C)}

3. \textbf{Administration of Intravenous Neostigmine and Monitoring}

3.1 Neostigmine 2 mg IV push is administered over 3 - 5 minutes.\(^2,6\) \textit{(Class I, Level B)}

3.2 Continuous presence of a physician knowledgeable in ACLS and a nurse in patient's room for 30 minutes after dose administration is required \textit{(Class I, Level C)}

3.3 Continuous telemetry monitoring for 30 minutes after dose administration is required to observe for bradycardia or asystole \textit{(Class I, Level C)}

3.4 Keep atropine at bedside \textit{(Class I, Level B)} Dose of atropine for symptomatic bradycardia is 1 mg intravenously as needed.\(^2\) \textit{(Class I, Level B)}

3.5 Monitor blood pressure over 15 minutes \(\times 2\) \textit{(Class I, Level C)}

3.6 Monitor respiratory rate and depth every 15 minutes \(\times 2\) \textit{(Class I, Level C)}

3.7 Patient should be kept supine, with a bedpan readily available \textit{(Class I, Level C)}

3.8 Crash cart kept immediately outside of patient's room \textit{(Class I, Level C)}

3.9 The safety and efficacy of neostigmine injection in the treatment of ACPO has not been established in children

3.10 The onset of action of intravenous neostigmine is 1 - 20 minutes, with duration of action of 1 - 2 hours. The average elimination half-life is 80 minutes, which is extended in patients with renal insufficiency.\(^11,12\)

4. \textbf{Contraindications}

4.1 Do not use neostigmine in the following conditions \textit{(Class III, Level C)}

4.1.1. Hypersensitivity to neostigmine

4.1.2. Baseline heart rate < 60 bpm or systolic blood pressure < 90 mm Hg

4.1.3. Uncontrolled arrhythmias

4.1.4. Mechanical intestinal or urinary tract obstruction

4.1.5. Signs of bowel perforation, ischemia, peritonitis, or acidosis

4.1.6. Renal insufficiency, serum creatinine > 3 mg/dl

4.1.7. Pregnancy

4.1.8. Severe bronchospasm

4.2 Use with caution in the following conditions \textit{(Class IIb, Level C)}

4.2.1. History of asthma or COPD
4.2.2. Epilepsy
4.2.3. Hyperthyroidism
4.2.4. History of cardiac arrhythmia such as atrial fibrillation and atrophicventricular block
4.2.5. Recent myocardial infarction (within the past 30 days)
4.2.6. Current beta blocker use
4.2.7. History of colon cancer
4.2.8. History of colon resection
4.2.9. Peptic ulcer
4.2.10. Vagotonia

5. Other Pharmacologic Agents
5.1 There are anecdotal reports of success using traditional prokinetic agents such as erythromycin, metoclopramide, and cisapride. The response rates were inconsistent for these agents, with only gradual improvement over 12 to 24 hours of therapy. (Class IIb, Level B)

6. Endoscopic Decompression
6.1 Should supportive and pharmacologic treatment fail, colonoscopic decompression has been successful in approximately 80% of patients with ACPO. (Class I, Level C)

UW Health Implementation
Potential Benefits:
1. Successful management of patients with ACPO with supportive therapy and intravenous neostigmine
2. Avoidance of complications of ACPO including colonic ischemia and perforation and associated morbidity
3. Avoidance of drug toxicity when using intravenous neostigmine

Potential Harms:
1. Safety information from using neostigmine for the treatment of ACPO is favorable; however, there are serious cautions to consider. Current clinical trials have required the presence of a physician for 30 minutes after the administration of injectable neostigmine for ACPO.

1.1. Serious Complications
1.1.1. Cardiovascular: Sinus cardiac arrhythmias (including atrophicventricular block, bradycardia, nodal rhythms, and nonspecific electrocardiogram changes), cardiac arrest and hypotension
1.1.2. Pulmonary: Bronchospasm, increased bronchial secretions, and respiratory depression
1.1.3. Hypersensitivity: anaphylaxis
1.1.4. Neurological: Seizures

1.2. Common Adverse Events

1.2.1. Cardiovascular: flushing and syncope
1.2.2. Gastrointestinal: emesis and nausea
1.2.3. Musculoskeletal: muscle cramps and spasms
1.2.4. Neurological: dizziness, drowsiness, dysarthria, headache, loss of consciousness, miosis, visual changes and weakness

Implementation Plan/Tools
This guideline has been developed based on best evidence recommendations. By implementing the parameters set forth in the guideline, patients will receive intravenous neostigmine appropriately and safely

1. Dosing guidelines will be built into Health Link to be visible upon order entry of intravenous neostigmine for ACPO
2. Education will be provided to health care providers as necessary
3. Guideline is available on “UConnect”
4. Education will be provided through Drug Policy Program (DPP) update

Disclaimer
This Clinical Practice Guideline provides an evidence-based approach for the treatment of ACPO. It is understood that the occasionally patients will not match the conditions considered in the guideline.

References


