Neuroanesthesia and Intensive Care

Best evidence in critical care medicine

Medical therapy of acute colonic pseudo-obstruction: a moving experience

Article appraised

Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999; 341: 137–41.

Structured abstract

Background: Acute colonic pseudo-obstruction is commonly encountered in both postoperative and nonoperative intensive care unit patients. It can result in complications ranging from nausea, to prolonged hospital stay, to cecal perforation. Until recently, there were no medical options when conservative treatments, such as normalizing electrolytes and minimizing opioids, failed. This meant that surgical or endoscopic decompression was often required. Data from non-controlled trials suggested that neostigmine could result in rapid improvement, leading to this higher-quality clinical trial.

Design: This was a randomized, double-blinded, placebo-controlled trial evaluating neostigmine for the treatment of acute colonic pseudo-obstruction.

Patients: 21 patients were recruited from medical and surgical wards at hospitals surrounding a single university centre. All patients had cecal diameters greater than 10 cm and had failed conservative therapy for 24 hr. Subjects had mechanical obstruction ruled out by the presence of air in the rectum on plain abdominal *x-ray*, or by radiographic contrast enema. Exclusion criteria included bradycardia, hypotension, intestinal perforation, asthma and recent use of prokinetic drugs. Baseline characteristics were similar between groups.

Intervention: Patients were randomized to receive a single dose of neostigmine 2 mg *iv*, or saline placebo. Patients had continuous cardiac monitoring due to concerns of bradycardia, which was treated with atropine as required. Patients in both groups were eli-

gible to receive open-label neostigmine after three hours if initial therapy failed.

Primary endpoint: A physician blinded to the assigned treatment assessed clinical response. This was divided into "immediate clinical response" (determined by passage of flatus or stool with reduction in abdominal distension within 30 min), as well as changes in clinical parameters after three hours (defined by abdominal circumference, colonic diameter). Treatment failures were defined as persistent or recurrent colonic distension, and the need for either open-label neostigmine, or for colonoscopic or surgical decompression.

Results: Ten of the 11 patients (91%) that received neostigmine, and none of the ten patients that received placebo, had an immediate clinical response ($P < 0.001$). Three of the neostigmine-treated patients were treatment failures: one because of lack of response, and two because of recurrence. One of these patients was successfully treated with a second, open-label dose. Open-label neostigmine was given to seven of the placebo-treated patients, and all had immediate clinical responses. Common side effects of neostigmine were predictable anticholinergic effects such as excess salivation, vomiting, abdominal pain and bradycardia. There were no serious side effects, but two patients (18%) required atropine for symptomatic bradycardia.

Conclusion: Neostigmine is effective for rapid resolution of acute colonic pseudo-obstruction.

Commentary by R.M. Penner, M.J. Jacka and P.G. Brindley

Initial management of acute colonic distension should focus upon ruling out mechanical obstruction, correcting reversible causes (particularly electrolyte abnormalities and hypothyroidism), and initiating conservative measures (frequent position changes,

nasogastric suction, fluid resuscitation, and minimization of exogenous opioids).¹ Of note, an enema with water-soluble, radio-opaque contrast medium can be both diagnostic and therapeutic. This is because the enema can both rule out true obstruction, and often stimulates colonic evacuation as a result of the hypertonic enema. Following these initial steps there were, until recently, few remaining medical options. Furthermore, although prokinetics such as metoclopramide, and colonoscopic decompression are frequently ordered, there is little evidence supporting these practices.

The above study by Ponc *et al.* built upon earlier uncontrolled reports of neostigmine's use in colonic pseudo-obstruction.² Despite very small sample sizes, this trial left little doubt of neostigmine's efficacy. Ponc reported a 91% initial treatment response, a 73% durable response, and a 100% response in the placebo-treated patients who were crossed over to open-label therapy. The relatively mild side effects are also reassuring. Unfortunately, a much larger study would be needed to determine if neostigmine is associated with rare but severe complications (ranging from cecal perforation to death). Reassuringly, however, a more recent review of neostigmine has not uncovered serious adverse reactions.³

The mechanism for postoperative ileus is not fully elucidated. However, it is likely exacerbated by both surgical activation of endogenous opioid receptors, and exogenous administration of opioid analgesics. As such, naloxone offers another potential strategy. Unfortunately naloxone's use is limited because of the potential to cause loss of analgesia or even opioid withdrawal.⁴ The desire to block the peripherally-mediated decreased gastrointestinal motility, but preserve the centrally mediated analgesia, has led to the study of a selective peripheral opioid receptor antagonist (ADL-8-2698).⁵ While also not a large study (79 patients), Taguchi *et al.* found a significantly more rapid return of flatus, bowel movement, and hospital discharge, and with no increased pain, using ADL-8-2698. However, this drug is not widely available, and is hence outside of most physicians' armamentarium.

Neostigmine should not be contemplated until mechanical obstruction has been ruled out. In addition, most postoperative colonic ileus is self-limiting, and typically resolves spontaneously within 72 hr. As such, the physician should be warned against routine neostigmine use. Furthermore, potential bradycardia means most protocols demand a monitored bed, and hence the therapy has administrative implications. The use of non-opioid analgesics such as non-steroidal anti-inflammatory drugs and local anesthetic epidurals, may also help avoid widespread use of neostig-

mine. Regardless, neostigmine can now be considered a viable option in the medical management of colonic pseudo-obstruction.

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