Use of neostigmine for acute colonic pseudo-obstruction in a patient receiving dexmedetomidine

Michelle M Dodds,Callum D Frazer, Jeffrey Lipman, Michael Reade

Acute colonic pseudo-obstruction is commonly encountered in intensive care, and its treatment may include neostigmine. Invasively ventilated patients are increasingly receiving dexmedetomidine as a combination sedative–analgesic. Bradycardia is a recognised, but rarely problematic, adverse effect of both medications. We are unaware of published reports of patients who have received these medications in combination, and we report such a case. A 64-year-old man was sedated with dexmedetomidine, which may have contributed to his development of acute colonic pseudo-obstruction. After he was started on neostigmine, profound bradycardia (heart rate of 25 beats per minute [bpm]) ensued, which resolved rapidly after administration of a single bolus of intravenous atropine. We suggest avoiding this combination of drugs in critically ill patients.

Clinical record

A 64-year-old man self-presented to us 9 days after a mechanical fall. He had been using opioids to manage his pain before admission. On presentation, he was in significant hypercapnic respiratory failure secondary to gross abdominal distension, with a P_{CO_2} of 70 mmHg. His medical history included mild autism, and he was an ex-smoker of 25 packs per year.

A computed tomography scan showed an unstable, three-column, ninth thoracic vertebral fracture; spinous process fractures of T7 to T9; and left 7th to 11th rib fractures. He also had bilateral inguinal hernias with a possibly incarcerated loop of bowel and dilated ascending and transverse colon. We were unable to reduce his hernias in the emergency department, so we admitted the patient for surgery. Subsequent bilateral open hernia repair excluded mechanical obstruction as the cause of his colonic distention. We therefore confirmed the diagnosis of acute colonic pseudo-obstruction (ACPO), which was likely to have been secondary to opioid use.

The patient was admitted to the intensive care unit, intubated and ventilated. As part of a multicentre randomised controlled trial of sedative strategies in mechanically ventilated patients, he was randomised to receive a dexmedetomidine infusion titrated to minimal effective sedation, with a maximal rate of 1 mg/kg/h. Suspected ACPO was not an exclusion criterion in this trial. His persisting gross abdominal distension and abdominal splinting resulted in ventilatory difficulty, specifically high peak pressures. Consequently, we decided to actively manage his ACPO.

In addition to regular aperients and electrolyte correction, the patient underwent colonoscopic decompression of his large bowel, which was partially successful in reducing his abdominal girth and improving ventilatory parameters. After no return of bowel sounds or bowel motions 24 hours later, neostigmine was used to facilitate gastrointestinal motility.

The patient was still receiving a dexmedetomidine infusion (0.8 mg/kg/h), and we were aware that dexmedetomidine and neostigmine can both cause bradycardia. Therefore, we administered neostigmine by slow intravenous (IV) infusion (2.5 mg over 5 hours), with staff available, continuous electrocardiographic monitoring and atropine at the bedside. We noted no bradycardia, hypotension or gastrointestinal effects, so we administered additional IV doses of neostigmine 1 mg over 20 minutes, followed by 2 mg IV over 20 minutes, according to our usual ICU protocol. During these infusions, brief episodes of sinus bradycardia (to a rate of 55 bpm) without associated hypotension were noted, and the patient's resting heart rate spontaneously returned to between 60 and 70 bpm. As the infusion was completed, the patient developed sinus bradycardia (heart rate, 25 bpm) and associated hypotension. We administered a 500 mg bolus of atropine, which successfully corrected his heart rate and haemodynamic compromise, and he had no subsequent episodes of bradycardia. The final 2 mg dose of neostigmine was effective in facilitating bowel opening, which we then supported with ongoing aperients.

The patient's ventilatory compromise resolved and he was successfully extubated, with his dexmedetomidine infusion ceased immediately before extubation. He continued to have between one and four bowel motions per day, with complete resolution of his ACPO, and needed no further neostigmine.

Poor pain control of the patient's rib and spinal fractures resulted in him developing basal lung collapse and consolidation, and hypercapnic respiratory failure. He was re-intubated on Day 5 of his ICU admission and had further dexmedetomidine sedation. He was treated with a 5-day course of piperacillin–tazobactam for *Haemophilus influenzae* respiratory infection. On Day 11 of his ICU admission, the patient underwent open fixation of his thoracic vertebral fractures, which aided with analgesia

and facilitated mobility for extubation. He was successfully extubated on Day 14 of his ICU admission, and discharged to the orthopaedic ward the following day.

Discussion

ACPO (Ogilvie syndrome) is a condition of disturbed colonic transit with dilation of the viscera, without evidence of mechanical obstruction. Its pathogenesis is thought to be an imbalance of increased sympathetic or decreased parasympathetic activity.[1] Predisposing factors include surgery, trauma, infection and organ failure; conditions which are commonly found in the ICU. General approaches to treatment include correction of underlying metabolic abnormalities, colonoscopic decompression and neostigmine. Surgical intervention is reserved for patients for whom medical therapies have failed or with suspected perforation.[2,3]

Highly selective a_2-adrenoreceptor agonists such as dexmedetomidine are being used increasingly in ICUs as prolonged-infusion, combination sedative–analgesics. Dexmedetomidine has the benefit of reduced cognitive depression compared with more traditional medications, and there is some evidence of fewer ventilator-dependent days without a reduction in the ICU length of stay.[4-7] Dexmedetomidine is up to eight times more selective than clonidine to a_2-adrenoreceptors.[4,8] a_2-Adrenoreceptors are located in many tissue types, but their primary role is at presynaptic sites, regulating neurotransmitter release via hyperpolarisation and suppression of neuronal firing, reducing catecholamine release. The locus coeruleus in the central nervous system is thought to be the major site of these actions, which result in analgesic and sedative effects.[4] This is likely not to be the only mechanism of action, as research in rats has shown direct inhibition of sodium channels in the dorsal horn, which could also be a cause of analgesia.[4,9]

The major adverse effects associated with dexmedetomidine are bradycardia (14%) and hypotension (20%), which occur more frequently than with other sedatives.[7] Effects on other tissues include decreased salivation and secretions, reduced bowel motility, reduced renin release, increased glomerular filtration, sodium and water retention, decreased intraocular pressure and decreased insulin release from the pancreas.[4]

Neostigmine is a peripherally acting anticholinesterase inhibitor, which increases the peak concentration and half-life of acetylcholine at the synaptic cleft, thus affecting nicotinic and muscarinic receptors. In patients with ACPO, it causes increased gastrointestinal motility and secretions, and has been shown to reduce the duration of the pseudo-obstruction.[10,11] Side effects include abdominal pain, and about 5% of neostigmine recipients have symptomatic bradycardia requiring atropine.[10,11] It is effective administered as a bolus and an infusion but the optimal regimen is unclear.[12,13]

α-Agonists play a role in the inhibition of intestinal motility, and there have been multiple case reports suggesting that clonidine is a contributing factor in the development of ACPO in post-operative and medically unwell patients.[14,15] In vitro studies in guinea pigs and rats have also shown that dexmedetomidine and clonidine inhibit intestinal peristalsis through their a_2-adrenoreceptor agonist effects on enteric neurons.[16,17] Studies in humans have shown that dexmedetomidine causes delayed gastric emptying and gastrointestinal transit.[18] Therefore, with the increasing use of dexmedetomidine sedation in the ICU, clinicians need to be aware of the dexmedetomidine-mediated reduction in bowel motility and the increased risk of ACPO.

Conclusion

ACPO is regularly encountered in the ICU, and neostigmine is one of the mainstays of treatment. With dexmedetomidine now being used more frequently for sedation and analgesia, clinicians must be aware of the potential limitations of using neostigmine in patients receiving dexmedetomidine infusions, most notably the risk of bradycardia.

Pharmacologically, the addition of neostigmine for the treatment of patients with ACPO receiving dexmedetomidine infusions is logical. Neostigmine increases parasympathetic activity of the gastrointestinal tract by inhibiting breakdown of acetylcholine, which may offset the a_2-adrenoreceptor-mediated suppression of peristalsis by dexmedetomidine.

As part of the management of ACPO in the ICU, clinicians should be aware of the contributory effect of a_2-adrenoreceptors such as dexmedetomidine, and consider ceasing their use. Our case study details our experience in judicious use of neostigmine to hasten the resolution of ACPO in a patient who continued to receive dexmedetomidine. We recommend a prudent initial regimen of a prolonged low-dose neostigmine infusion with continuous monitoring for bradycardia, skilled nursing and medical staff on standby, and atropine at hand. Bolus doses of neostigmine should be avoided for patients receiving dexmedetomidine.

Author details

Michelle M Dodds, Registrar[1]

Callum D Frazer, Registrar[1]

Jeffrey Lipman, Director,[1] Professor and Head of Anaesthesiology and Critical Care,[2] and Adjunct Professor[3]

Michael Reade, Staff Specialist,[1] Professor of Military Medicine and Surgery,[2] and Lieutenant Colonel[4]

1 Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.

2 School of Medicine, University of Queensland, Brisbane, QLD, Australia.
3 Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia.
4 Royal Australian Army Medical Corps, ADF Joint Health Command, Australia.
Correspondence: michelle.dodds@health.qld.gov.au

Competing interests

None declared.

References

1 Saunders MD, Kimmey MB. Systematic review: acute colonic pseudo-obstruction. *Aliment Pharmacol Ther* 2005; 22: 917-25.
2 De Giorgio R, Knowles CH. Acute colonic pseudo-obstruction. *Br J Surg* 2009; 96: 229-39.
3 Pereira P, Djeudji F, Leduc P, et al. Ogilvie's syndrome — acute colonic pseudo-obstruction. *J Visc Surg* 2015; 152: 99-105.
4 Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative–analgesic agent. *Proc (Bayl Univ Med Cent)* 2001; 14: 13-21.
5 Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; 301: 489-99.
6 Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; 298: 2644-53.
7 Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012; 307: 1151-60.
8 Holliday SF, Kane-Gill SL, Empey PE, et al. Interpatient variability in dexmedetomidine response: a survey of the literature. *Scientific World Journal* 2014: 805013.
9 Gu X-Y, Liu B-L, Zang K-K, et al. Dexmedetomidine inhibits tetrodotoxin-resistant Nav1.8 sodium channel activity through Gi/o-dependent pathway in rat dorsal root ganglion neurons. *Mol Brain* 2015; 8: 15.
10 Kayani B, Spalding DR, Jiao LR, et al. Does neostigmine improve time to resolution of symptoms in acute colonic pseudo-obstruction? *Int J Surg* 2012; 10: 453-7.
11 Valle RGL, Godoy FL. Neostigmine for acute colonic pseudo-obstruction: a meta-analysis. *Ann Med Surg* 2014; 3: 60-4.
12 White L, Sandhu G. Continuous neostigmine infusion versus bolus neostigmine in refractory Ogilvie syndrome. *Am J Emerg Med* 2011; 29: 576.e1-3.
13 Abeyta BJ, Albrecht RM, Schermer CR. Retrospective study of neostigmine for the treatment of acute colonic pseudo-obstruction. *Am Surg* 2001; 67: 265-8; discussion 268-9.
14 Stieger DS, Cantieni R, Frutiger A. Acute colonic pseudoobstruction (Ogilvie's syndrome) in two patients receiving high dose clonidine for delirium tremens. *Intensive Care Med* 1997; 23: 780-2.
15 Bear R, Steer K. Pseudo-obstruction due to clonidine. *Br Med J* 1976; 1: 197.
16 Sagrada A, Fargeas MJ, Bueno L. Involvement of alpha-1 and alpha-2 adrenoceptors in the postlaparotomy intestinal motor disturbances in the rat. *Gut* 1987; 28: 955-9.
17 Herbert MK, Roth-Goldbrunner S, Holzer P, Roewer N. Clonidine and dexmedetomidine potently inhibit peristalsis in the Guinea pig ileum in vitro. *Anesthesiology* 2002; 97: 1491-9.
18 Iirola T, Vilo S, Aantaa R, et al. Dexmedetomidine inhibits gastric emptying and oro-caecal transit in healthy volunteers. *Br J Anaesth* 2011; 106: 522-7. ❑