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Intravenous and Subcutaneous Administration of Neostigmine for Acute Colonic Pseudo-Obstruction: A Short Review

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Abstract

Acute Colonic Pseudo-Obstruction (ACPO), also known as Ogilvie's Syndrome, is a rare postsurgical complication characterized by acute dilation of the colon without anatomical obstruction. Neostigmine is increasingly used to manage ACPO when conservative measures fail. Intravenous neostigmine has historically been favored for its rapid onset and effectiveness; however, it can cause adverse effects, particularly bradycardia, necessitating close cardiac monitoring. Recently, subcutaneous neostigmine has gained popularity due to fewer reported adverse events, thus requiring less intensive monitoring according to many guidelines. There is limited literature directly comparing intravenous and subcutaneous neostigmine in patients with ACPO. Given the emerging role of subcutaneous neostigmine and the current gap in clinical practice, we conducted a thorough literature review to compare the safety and effectiveness of intravenous and subcutaneous neostigmine in patients with ACPO.

Keywords: Neostigmine; Large bowel obstruction; Colorectal surgery; General surgery; Ogilvie's syndrome.

Introduction

Acute Colonic Pseudo-Obstruction (ACPO), also known as Ogilvie's Syndrome, is characterized by acute dilation of the colon without an anatomical obstruction. Symptoms include abdominal tenderness, distension, nausea, and acute changes in bowel habits [1]. ACPO is a rare post-surgical complication, occurring in only 0.1% of the inpatient population, as demonstrated in a large national study [2]. Elderly males are at an elevated risk, with the prevalent age range being 65 to 81 years [2,3]. Surgery, particularly intra-abdominal and pelvic procedures, is a major risk factor for ACPO, further exacerbated by the use of medications commonly administered to surgical patients, such as opioids and anticholinergics [4-7].

Abdominal Computed Tomography (CT) is essential for diagnosing ACPO, as it reveals significant colonic dilation without an obstructing lesion. Transition zones are most commonly found near the splenic flexure and are often gradual rather than abrupt, with the small bowel usually not involved [8]. If ACPO is not rec-

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ognized and treated promptly, it can lead to fatal complications, such as bowel ischemia and perforation, with reported mortality rates of up to 44% [1,2].

Historically, intravenous administration of neostigmine has been the preferred treatment due to its fast onset of action, excellent efficacy, and predictable pharmacodynamics. However, intravenous neostigmine has drawbacks, including short duration of action, risks of hemodynamic instability, and the need for close cardiovascular monitoring, often requiring Intensive Care Unit (ICU) or coronary care unit admission [9]. On the other hand, subcutaneous administration of neostigmine has been increasingly reported in the literature and can be administered in a ward environment with promising results [9,10]. To date, there have been limited studies or reviews specifically discussing the role of subcutaneous neostigmine in managing ACPO, and direct comparisons between intravenous and subcutaneous administration are lacking. This review aims to explore the safety and efficacy of subcutaneous neostigmine in patients with ACPO, providing a comprehensive analysis of the current evidence.

General management of ACPO

In general, less than 10% of patients with ACPO require endoscopic or surgical decompression, as the majority can be managed medically [2]. A stepwise approach to managing ACPO, beginning with conservative measures, is therefore recommended [11]. The conservative measures include fasting, decompression with a nasogastric tube, volume repletion, cessation of opioids and anticholinergic medications, and correction of electrolyte imbalances, particularly potassium and magnesium. Conservative management has demonstrated success rates of 77% to 96% [12,13].

The use of neostigmine represents a significant advancement in the management of ACPO and is the recommended pharmacologic therapy for patients who do not respond to conservative measures after 48-72 hours of conservative management or have marked caecal distention (>10 cm) of significant duration (>3-4 days) [11,14]. It is an acetylcholinesterase inhibitor, marked a significant advancement in the management of ACPO because of its safety and effectiveness in achieving colonic decompression, with initial response rates of 6090% [15]. The typical dosage is 2 mg administered intravenously over 3-5 minutes [11]. The use of neostigmine will be further discussed in the next part.

Patients who fail conservative management, cannot tolerate neostigmine, or for whom neostigmine is otherwise contraindicated, and who experience recurrent ACPO episodes, usually require endoscopic decompression or surgical intervention. The procedure involves the insertion of a colonoscope to relieve colonic distension by evacuating gas and stool. It has a high response rate of approximately 80% [15]. Historically, surgical interventions like cecostomy and colectomy were the primary treatments for ACPO. Since patients with ACPO are usually comorbid and critically ill, these procedures had a high overall mortality rate of 30% during the “preneostigmine era” [1]. Currently, surgery is only required if patients present with signs or symptoms of perforation or ischemia, to assess bowel viability and perform resection or repair, or for patients not responding to medical management and endoscopic decompression [6].

Neostigmine

Pathophysiology of ACPO and neostigmine

The use of neostigmine in treating ACPO is closely linked to the condition’s proposed pathophysiology. ACPO is currently understood to be an autonomic disorder characterized by a significant imbalance between sympathetic and parasympathetic tones, predominantly affecting critically ill patients who exhibit an increased sympathetic drive [16]. The sympathetic innervation to the colon, which decreases motility, is via the celiac and mesenteric ganglia. Parasympathetic fibers, originating from S2 to S4, are responsible for facilitating the emptying of the left colon and rectum. Since the vagal supply to the large bowel terminates at the splenic flexure and the parasympathetic innervation of the left colon originates from the sacral plexus, it is proposed that transient impairment of parasympathetic function at the sacral plexus may cause atony of the distal large bowel, leading to functional obstruction.

The peripheral nervous system is composed of the autonomic and somatic nervous systems. The autonomic system can be further divided into the parasympathetic and sympathetic nervous systems. The parasympathetic nervous system regulates various organs and primarily uses acetylcholine as its main neurotransmitter. Acetylcholine’s peripheral actions are mediated through two types of receptors: muscarinic (M_1, M_2, M_3, M_4, M_5) and nicotinic (N_m, N_n) receptors [17]. Acetylcholine is metabolized by acetylcholinesterase, which hydrolyzes acetylcholine at the neuromuscular junction. Neostigmine, an acetylcholinesterase inhibitor, increases the concentration of circulating acetylcholine at the neuromuscular junction. This enhances parasympathetic drive and subsequently increases the contractility of the colonic smooth muscle [11].

However, increased parasympathetic drive can negatively impact chronotropy and inotropy. Therefore, intravenous neostigmine should only be administered with continuous cardiac monitoring, such as in an ICU setting, for early detection and management of bradycardia and other arrhythmias [11]. Besides its cardiovascular effects, other side effects of neostigmine include muscle weakness: intravenous administration of a therapeutic 2.5 mg dose has been found to decrease hand grip strength by 20% after the first dose and by 41% after the second dose within 15 minutes, compared to the placebo group. Gastrointestinal side effects include cramping, nausea, vomiting, and sialorrhea. Respiratory complications, particularly respiratory distress with a restrictive pattern, such as bronchospasm, can occur. Additionally, although, neostigmine does not readily cross the blood-brain barrier, general and nervous system disorders such as dizziness and headache, as well as pruritus, have been reported [9,18,19].

Pharmacokinetics of neostigmine

Neostigmine can be administered either intravenously or subcutaneously. Subcutaneous administration results in slower absorption compared to intravenous administration, as reflected in the longer average response times of patients shown in the tables below. While there have been no studies on the T_{max} in human, studies in animal models (horses) show a median T_{max} of 20 minutes [20]. After absorption, the volume of distribution for neostigmine ranges from 0.12 to 1.4 L/kg, although there have been no studies on the volume of distribution for subcutaneous injections

[21]. Neostigmine is metabolized by microsomal enzymes in the liver, with a half-life ranging from 24 to 113 minutes. Total body clearance is reported to be between 1.14 and 16.7 mL/min/kg. In patients with renal impairment, the elimination half-life is prolonged. For example, in anephric patients, the half-life can extend to 181±54 minutes, compared to 79.8±48.6 minutes in individuals with normal renal function [21].

Intravenous and subcutaneous neostigmine in ACPO

To date, there are no randomized controlled trial data comparing intravenous and subcutaneous neostigmine in patients with ACPO, nor is there clear guidance on patient selection for a particular route of administration. In small interventional and observational studies (Table 1), the rapid onset of action of intravenous neostigmine, which raises body acetylcholine levels, has been consistently associated with rapid symptom resolution, usually within minutes to hours [22-26]. Conversely, subcutaneous administration of neostigmine works by creating a depot, leading to a slower absorption rate and a more gradual increase in acetylcholine levels. A multicenter study by Kram et al. involving 182 patients found that the median time to the first bowel movement following initiation of subcutaneous neostigmine was 29.19 hours [27]. Additionally, because rapid symptom resolution is expected with intravenous neostigmine, patients who are likely to fail medical management can be identified early and escalated to endoscopic or surgical treatment as needed.

As summarized in Table 1, the most concerning complication of intravenous neostigmine, bradycardia requiring atropine, occurs in approximately 10% of patients. Strategies such as dose reduction, co-administration of atropine, and using infusion rather than bolus administration have been proposed in the literature. While these approaches may theoretically enhance safety, their efficacy and safety in ward settings have not been conclusively established [23,28-31]. According to current guidelines and local protocols [9,14], patients receiving intravenous neostigmine require close cardiopulmonary monitoring that allows for immediate support and treatment in the event of bronchospasm or bradycardia. Additionally, factors such as ICU bed availability, costs to the hospital system, and potential delays in receiving treatment should be considered. On the other hand, subcutaneous administration of neostigmine results in a slower increase in acetylcholine levels. This slower pharmacokinetic profile reduces the risk of sudden, severe cardiovascular effects, making continuous cardiac monitoring less critical. In the study by Kram et al., the rate of bradycardia was only 1% (2/182), and the bradycardia resolved after discontinuation of the medication [27]. In Frankel et al.'s study, none of the 30 patients receiving subcutaneous neostigmine experienced symptomatic bradycardia, and 93% (28/30) of the patients passed stool or flatus within two days [32]. Therefore, it may be reasonable to conclude that patients with robust baseline cardiovascular function and those at imminent risk of fatal complications from ACPO, or those already in a clinical environment with continuous cardiac monitoring, may be the best candidates for intravenous neostigmine. Regardless, a prospective study delineating suitable ACPO patients for various routes of neostigmine administration and informing future guidelines is urgently needed.

Table 1: Studies investigating effects of intravenous and subcutaneous neostigmine on ACPO (Acute Colonic Pseudo-Obstruction).

Author (s)	Year	Study type	Sample and sample size	Diagnostic and treatment criteria for ACPO	Route of neostigmine	Dose of neostigmine	Outcomes	Complications of neostigmine
Ponec et al. [22]	1999	Prospective, double-blind, placebocontrolled trial	11 patient received neostigmine; 10 patient received placebo)	Radiological signs of ACPO with cecal diameter >10 cm No response to conservative treatment >24 hr	Intravenous	2 mg over 3-5 mins	91% (10/11) of the interventional cohort had prompt colonic decompressions. Median time to response was 4 min. 18% (2/11) required colonoscopic depression for recurrent ACPO.	Abdominal pain: 73% (8/11) Sialorrhoea: 27% (3/11) Vomiting: 9% (1/11) Bradycardia[b]: 9% (1/11)
Turégano-Fuentes et al. [23]	1997	Prospective, observational study	16 patients received neostigmine	Median cecal diameter of 12 cm with the maximum diameter of 25 cm No response to a varying period of conservative treatment	Intravenous	2.5 mg in 100 ml of normal saline for 60 mins	75% (12/16) of the cohort decompression with a single dose. 6% (1/16) had a complete resolution after second dose. 19% (3/16) patients had partial improve. The response time varied between 20 min to 4hrs.	Bradycardia: 6% (1/16)
Amaro et al. [24]	2000	Prospective, randomized, double-blind, placebocontrolled study	10 patient received neostigmine; 10 patient received placebo with 8 cross-over received neostigmine	Radiological signs of ACPO with cecal diameter >10 cm No response to conservative treatment >24 hr	Intravenous	2 mg over 3-5 mins	100% (10/10) of the neostigmine cohort had an immediate clinical response after injection (median response time 4 min), 27% patients (in the neostigmine group and eight (80%) in the placebo group failed to show sustained improvement 3 h after infusion.	Abdominal pain: 72% (13/18) Bradycardia: 11% (2/18)

Abeyta et al. [25]	2001	Retrospective observational study	8 patients received neostigmine for ten episodes of ACPO	Clinical and radiological signs of ACPO Treatment criteria not specified	Intravenous	2 mg bolus	Average 22.8±13.5 min response time in 6 episodes after first neostigmine dose. Average 44.7±37.7 min response time in 3 other episodes after second dose. During 1 episode, a patient received 2 doses of 1 mg and achieved resolution.	Bradycardia: (1/8)	12.5%
Paran et al. [26]	2000	Prospective, observational study	11 patients received neostigmine	Clinical and radiological signs of ACPO Treatment criteria not specified	Intravenous	2.5 mg in 100 mL saline over 60 mins	82% (9/11) of the patients had spontaneous colonic decompression. One patient had partial resolution after injection and complete resolution within 24 hrs. No effect was observed in one patient who required colonoscopic decompression. Of the nine patients with complete resolution, seven (78%, 7/8) passed flatus between 20 to 70 minutes from the beginning of the first dose of neostigmine infusion. The other two patients had spontaneous decompression of the colon after a second dose, administered 2 hours after the first dose.	No adverse reported	events
Loftus et al. [13]	2002	Retrospective observational study	18 patients received neostigmine	Radiological signs of ACPO with cecal diameter >10 cm No response to conservative treatment	Intravenous	2 mg over 3-5 mins	16 patients (89%) had prompt evacuation (<30 min) of flatus or stool. Sustained clinical response to neostigmine was noted in 11 of 18 (61%). Seven patients (39%) required colonoscopic decompression or surgery for recurrent or persistent colonic dilation.	Bradycardia: 11% (2/18) Prevalences of other adverse events including abdominal pain, excess salivation, and vomiting not reported	
Fanaei et al. [29]	2008	Prospective, interventional study	21 patients received neostigmine	Radiological signs of ACPO with average cecal diameter is 12.5 cm Treatment criteria not specified	Intravenous	2.5 mg in 250 mL saline for 30 min	95% (20/21) passed stool or gas after first dose. 17% decrease in cecal diameter after 3 hours of treatment.	Abdominal pain: 43% Sialorrhoea: 38% Vomiting: 19% (4/21) Bradycardia: 5% (1/21)	
Kram et al. [27]	2018	Multicenter, etrospective observational study	20 patients with ACPO received neostigmine[a]	Radiological and clinical signs of ACPO Treatment criteria not	Subcutaneous and intravenous as rescue	0.2-1 mg with various frequenc y from once to 4 times and more.	34 hrs median time for first bowel movement time for patients with ACPO; 5% (1/20) received intravenous neostigmine as rescue medication.	14% (25/185) of the patients experienced adverse events including bradycardia (1%, 2/185), nausea, and severe diarrhoea.	
Frankel et al. [32]	2019	Retrospective case series	30 patients received neostigmine	Radiological and clinical signs of ACPO with mean caecal diameter of 8.7 cm All patients received conservative treatment	subcutaneous	0.5 mg up to 3 times daily	93% (28/30) of the patients passed stool or flatus within 2 days of receiving neostigmine. 7% (2/30) of the patients underwent endoscopic decompression. Median number of doses was 6 and median duration of treatment was 3 days	No serious adverse effects reported.	
Kim et al. [33]	2021	Multicenter, retrospective observational study	31 patients received neostigmine	Radiological and clinical signs of ACPO No response to conservative treatment.	Intravenous and subcutaneous	0.25, 0.5, 1, 2 mg, additional dose required if ACPO recurred	100% clinical response for both subcutaneous and intravenous after 1 dose (bowel movement at median of 120 minutes after neostigmine). Patients received subcutaneous neostigmine required more repeated injection.	Sweating: 3% (1/31) Sialorrhoea: 3% (1/31) Vomiting: 3% (1/31) Bradycardia: 3% (1/31)[c]	

Conclusion

In conclusion, subcutaneous injection of neostigmine has a lower adverse event rate but a longer response time in patients with ACPO, whereas intravenous injection has a higher adverse event rate but a shorter response time. Although there is a lack of randomized controlled trial data comparing the clinical outcomes of subcutaneous and intravenous neostigmine, both routes can be reasonable and safe options for patients with ACPO, depending on the clinical urgency and available resources within the facility. Prospective studies and future guidelines are needed to clarify patient selection and dosage, particularly for subcutaneous neostigmine, in this high-risk patient population.

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