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ORIGINAL

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Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure – a prospective, double-blind, placebo-controlled trial

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Abstract *Objective*: Critical illness-related colonic ileus (CIRCI) is characterized by the non-passage of stools in critically ill patients as a result of the absence of prokinetic movements of the colon, while the upper gastrointestinal tract functions properly and mechanical ileus is absent. We investigated whether neostigmine resulted in defecation in patients with CIRCI.
Design: Double-blinded, placebo-controlled prospective study.
Setting: Eighteen-bed intensive care unit.
Patients: Thirty ventilated patients with multiple organ failure with CIRCI for > 3 days.
Intervention: Continuous intravenous administration of neostigmine 0.4–0.8 mg/h over 24 h, or placebo.
Measurements and results: Time to first defecation and adverse reactions were recorded. Thirty patients were randomized, 24 could be evaluated. The mean prestudy time was 5 days, mean APACHE II score on admission was 23.2, and mean MOF score on the day of the study was 6.4. Of the 13 patients receiving neostigmine, 11 passed stools, whereas none of the placebo-treated patients passed stools ($P < 0.001$). After 24 h, the non-responders received in a cross-over fashion neostigmine or placebo respectively. Eight out of the 11 neostigmine patients now passed stools (mean 11.4 h), and none of the placebo patients. Overall, in none of the patients did passage of stools occur during placebo infusion, whereas 19 of the 24 neostigmine-treated patients had defecation (79%). No acute serious adverse effects occurred, but three patients had ischemic colonic complications 7–10 days after treatment.
Conclusion: Continuous infusion of 0.4–0.8 mg/h of neostigmine promotes defecation in ICU patients with a colonic ileus without important adverse reactions.

Key words Critical care · Ileus · Neostigmine · Prokinetics · Gastrointestinal motility · Selective decontamination of the digestive tract

Introduction

In critically ill patients, gastrointestinal motility is often disturbed [1]. Traditionally, most emphasis is placed on dysmotility of the upper digestive tract. However, the stomach and small intestines may function properly while at the same time an isolated paralysis of the colon exists. This critical illness-related colonic ileus (CIRCI) is found in critically ill medical as well as surgical patients, in the latter after both non-abdominal surgery and after laparotomy with or without opening of the gut. CIRCI is characterized by the non-passage of stools for prolonged periods without gastric retention and with normal findings during physical and radiological examination – in contrast to adynamic ileus, in which abdominal distension and vomiting are found, and Ogilvie's syndrome, in which a dilated colon is paramount. Proposed mechanisms for CIRCI are the administration of

morphinomimetics and adrenergic agents [2, 3, 4], a low-flow state resulting in ischemia [5], endotoxemia [6], elevated levels of nitric oxide (NO) [7, 8], or a combination of these factors. An ileus in critically ill patients prohibits enteral feeding and promotes bacterial overgrowth and translocation of bacteria and absorption of endotoxins [9]. It further prohibits adequate selective decontamination of the digestive tract (SDD) because the non-absorbable antibiotics do not reach the rectum. Untreated ileus may ultimately lead to distension of the colon, increasing the risk of colonic wall ischemia and perforation [10, 11].

Neostigmine is a cholinesterase-inhibitor, which augments the concentration of acetylcholine (ACh) at the neuromuscular junction, thereby increasing contractions in the normal gut [8]. Since defecation might be beneficial for the patient, as it removes bacteria and endotoxins [12, 13], a double-blind, placebo-controlled trial was undertaken to investigate whether continuous intravenous administration of neostigmine results in defecation in critically ill patients with an ileus of the colon.

Material and methods

Patients

After approval by the hospital's scientific and ethical committee, 30 consecutive patients were enrolled in the study, after written informed consent was obtained from their legal representatives. Inclusion criteria were: no production of stools in a mechanically ventilated patient with normal or diminished peristalsis, after more than 3 days of intensive care treatment including enteral feeding and clysmata. Exclusion criteria were: expected death within 7 days, expected discharge from the ICU within 2 days, signs or symptoms of an acute abdomen, mechanical ileus or Ogilvie's syndrome diagnosed by physical and radiological examination, gastrointestinal surgery less than 10 days prior to inclusion, atrial-ventricular conduction disturbances, and sinus bradycardia < 60 BPM or a nodal rhythm.

Intensive care treatment

Patients were treated according to our standard therapeutic protocols. Circulatory support consisted of dopamine and vasodilators (nitroglycerin, ketanserin, or a combination). Enoximone was added in case of persistent low cardiac output in spite of optimal filling pressures and titrated therapy with dopamine and vasodilators. An intra-aortic balloon pump was inserted in case of persistent cardiac failure. Selective decontamination of the digestive tract was accomplished by administration of q.i.d. the non-absorbable antibiotics tobramycin 80 mg, polymyxin B 100 mg and amphotericin B 500 mg as a solution via the nasogastric tube, and q.i.d. application of a 2 % concentration of each of the antibiotics in a sticky paste (Orabase) in the oral cavity [14]. Enteral feeding via a nasogastric tube was administered in all patients, aimed at covering full calorie and protein requirements. Cisapride was added in case of gastric retention, at > 500 ml/24h, and lactulose and enemas were given when defecation did not occur once a day. Analgesia and sedation were given as needed with intravenous boluses of morphine and diazepam of 5–10mg, or with morphine and midazolam as a continuous infusion. Neuromuscular blocking agents were only given to facilitate intubation of the trachea and during surgery.

Protocol

Indistinguishable syringes containing neostigmine (5 mg in 50 ml NaCl 0.9 %) or placebo (50 ml NaCl 0.9 %) were produced by the hospital pharmacy. The infusion was started at 4 ml/h (i.e. 0.4 mg neostigmine/h, or placebo). If no stools were produced after 8 h the infusion rate was doubled. The primary endpoint was the estimated production of more than 100 ml of stools. Secondary endpoints were the need for discontinuation of the study medication due to prolongation of the PQ-interval on the EKG, painful abdominal cramping, or excessive production of saliva or sputum. A second study period was instituted in patients not passing stools after receiving the trial medication for 24 h. These non-responders received placebo if the first study medication had been neostigmine, and vice versa, while the same double-blind protocol for administration was followed.

Measurements

Every 3 h, the passage of stools, the volume of gastric retention, and the amount of administered enteral feeding was noted by the nurses. The severity of abdominal cramping was assessed by pain or agitation of the patient as absent, minor, or severe. The heart rate and rhythm were continuously recorded, the PQ interval was measured on a daily EKG, and an additional EKG was made in case of suspected rhythm or conductance disturbances. The amount of sputum was graded at least every 6 h on a subjective scale (normal, much, excessive), as was the amount of saliva. Severity of disease was quantified by the APACHE II score over the first 24 h after ICU admission [15]. Severity of multiple organ failure at the time of randomization was graded by the Goris score, attributing 0, 1 or 2 points to each of seven organ systems, to a maximum of 14 [16]. Patients were followed until discharge from the hospital or death, and complications that were possibly related to neostigmine were recorded.

Data analysis

Values are presented as mean and 95 % confidence interval (CI) or as median and interquartile range (IQ) for non-parametric data. The two-sided Fisher's exact test was used to compare nominal variables, the two-tailed Mann-Whitney test for continuous values.

Results

Thirty patients were randomized. One had to be excluded because of emergency surgery before the study medication was started. The records of five patients were lost due to a fire. So, 24 patients were evaluable, and their characteristics are summarized in Table 1. No significant differences were found between the patients receiving neostigmine or placebo (Table 2). Two patients died during their stay in the ICU, and six died after discharge from the ICU. No patient received adrenaline or noradrenaline prior to, during, or after the study.

Table 1 Patient characteristics at study entry. *Days* are days after admission to ICU. *Spec* is the admitting specialty – *m* medical, *c* cardiac surgical, *s* surgical. *AII* is the APACHE II score on ICU admission. *Goris* represents points according to the Goris MOF score on the day of inclusion. *Morph* received *(Y)* or did not receive *(N)* morphine in the 24 h before start of the study medication. *Dopa* dopamine (μg/kg/min) at time of inclusion. *LCO* low cardiac output, *MVI* mitral valve incompetence, *CABG* coronary bypass grafting, *VSR* ventricular septum rupture, *AVR/MVR* aortic/mitral valve replacement, *polytransfusion* received > 8 units of packed cells in the first 24 h after admission, *COPD* chronic obstructive pulmonary disease, *DIC* diffuse intravascular coagulopathy, *rAAA* ruptured abdominal aortic aneurysm, *ARF* acute renal failure, *VF* ventricular fibrillation

Patient	Age, years	Spec	Diagnosis	Days	AII	Goris	Morph	Dopa
1	72	m	LCO/MVI/ARF	5	26	6	Y	8
2	74	c	CABG/LCO/Mediastinitis	8	19	6	N	4
3	75	c	CABG/Correction VSR/LCO	9	19	10	N	22
4	73	m	LCO	5	36	5	N	5
5	73	m	Myocardial infarction/LCO	5	17	6	N	4
6	71	c	Pericardectomy/LCO	4	20	4	N	16
7	69	c	AVR/LCO	6	13	7	N	11
8	63	c	MVR/correction VSR/LCO	6	20	7	N	15
9	46	c	Pneumonia/emergency CABG/LCO	5	7	3	N	3
10	63	s	Polytransfusion/liver cirrhosis Child C	3	28	9	N	8
11	76	m	Pneumonia/septic shock/COPD	3	24	4	Y	4
12	74	c	CABG/LCO	4	19	8	Y	17
13	37	m	Pneumonia/septic shock	3	21	7	Y	4
14	67	m	Meningitis/septic shock	5	30	5	N	4
15	76	c	CABG/LCO/Polytransfusion	6	18	5	N	16
16	64	m	Endocarditis/septic shock/DIC	6	37	10	N	16
17	66	s	Hemihepatectomy/polytransfusion	3	23	5	N	6
18	73	s	rAAA/Polytransfusion/ARF	5	22	9	N	12
19	69	m	Pneumonia/septic shock/LCO	4	32	4	N	8
20	72	c	CABG/LOS/Polytransfusion/ARF	5	19	8	N	10
21	47	m	Cirrhosis/pneumonia/cardiac arrest	4	38	12	N	4
22	64	m	Meningitis/septic shock	6	22	5	N	4
23	69	c	CABG/Polytransfusion/pneumonia/ARF	4	16	4	N	9
24	68	m	Ischemic VF/LCO	5	30	4	N	8

Table 2 Comparison of patients receiving neostigmine or placebo. The differences are not significant. Data are presented as mean (95 % confidence interval) *(CI)*. *AII* APACHE II score on ICU admission, *MOF* points according to the Goris MOF score on the day of inclusion, *Morph* number of patients who received morphine in the 24 h before start of the study medication, *Dopa* dopamine (μg/kg/min) at time of inclusion

Parameter	Neostigmine	Placebo
Number	13	11
Age (years)	66.0 (59.1–72.9)	67.5 (61.8–73.3)
AII	22.7 (18.8–26.6)	23.7 (17.5–29.9)
MOF	7.1 (5.9–8.4)	5.5 (3.9–7.2)
Morph	3	1
Dopa	8.3 (5.5–11.1)	10.0 (5.8–14.2)

All patients received enteral nutrition at a rate of at least 1,000 ml/day via a nasogastric tube – no patient had gastric retention of more than 500 ml/24 h.

Effects of neostigmine

Eleven out of the 13 verum patients passed stools, and none of the 11 placebo patients ($P < 0.001$) (Fig. 1). The produced volume of the feces was per definition at least 100 ml, but in most cases much more, estimated up to over 1,000 ml in many. The median time to defecation after the start of the study medication was 6 h (IQ 4–9 h). Thirteen patients, not having passed stools during the first 24 h, received the second study drug: 11 received neostigmine, and two received placebo. In this second study period, eight of the neostigmine patients passed stools after a median of 12 h (IQ 5–18 h), but none of the placebo patients did. Overall, none of the patients passed stools during placebo infusion, whereas passage of stools occurred in 19 of the 24 neostigmine-treated patients (79 %). There was no difference in APACHE II, MOF scores (Goris), number of patients receiving morphine, or hospital mortality between responders and non-responders to neostigmine. Dopamine dosage was higher in the non-responders, but the difference was not significant ($P = 0.13$) (Table 3).

Secondary endpoints and complications

In none of the patients did the infusion have to be stopped or reduced because of adverse effects, although in three patients a clinically not relevant increase in saliva

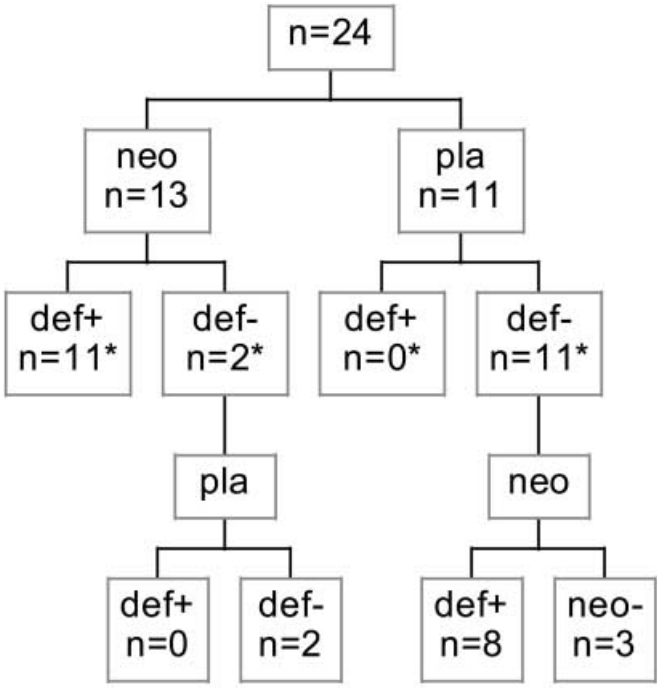

Fig. 1 Results. (* Neostigmine vs. placebo: $P < 0.001$, *n* number of patients, *neo* neostigmine, *pla* placebo, *def+* defecation within 24 h, *def–* no defecation within 24 h)

Table 3 Comparison between responders and non-responders. No significant difference exists between the variables. Data are presented as mean (95% confidence interval) *(CI)* or median (25–75% interquartile range) *(IQ)*. For colon complication, see text. *AII* APACHE II score on admission, *MOF* points according to the Goris MOF score on the day of inclusion, *Dopa* dopamine (μg/kg/min) at time of inclusion, *Morph* number of patients who received morphine in the 24 h before start of the study medication, *Died* hospital mortality

Parameter	Responders	Non-responders
Number	19	5
Age (years)[a]	67.0 (63.0–71.0)	65.6 (45,4–85.8)
AII[a]	23.5 (19.5–27.4)	22 (14.9–29.1)
MOF[a]	6.5 (5.3–7.6)	6.0 (2.8–9.2)
Dopa[b]	8.0 (4–10.5)	16 (6–19)
Morph	3	1
Died *(n)*	6	2
Colon complication *(n)*	2	1

[a] Mean (95% CI)
[b] Median (25–75% IQ)

and sputum production was noted. No rhythm or conductance disturbances occurred during the infusion of the study medication. Three of the patients had late colonic complications more than 7 days after the start of the study medication. The first (no. 6) was a patient with multiple organ failure due to low cardiac output after surgical relief of pericarditis constrictiva. He had not responded to placebo or (after cross-over) to neostigmine, and underwent a hemicolectomy because of caecal perforation, 7 days after inclusion – he survived. The second patient (no. 12), who had responded to neostigmine, suffered from multiple organ failure due to low cardiac output after cardiac surgery. He was successfully treated without surgical intervention for an ischemic colitis as assessed by colonoscopy on day 10 after inclusion. The third colonic complication occurred in a patient (no. 16) with endocarditis with multiple organ failure. He did not respond to placebo but had passed stools after cross-over to neostigmine, and died with intestinal necrosis on day 7 after inclusion. No differences were found in APACHE II and Goris scores between patients with and patients without colonic complications. However, the median dopamine dose was significantly higher in the patients with colonic complications (16, IQ 16–16.5 vs. 8.0, IQ 4–10.5 μg/kg/min, $P = 0.015$).

Discussion

This double-blind, placebo-controlled study shows that the continuous intravenous administration of neostigmine 0.4 to 0.8 mg/h results in defecation in critically ill, ventilated patients with an ileus of the colon. Eleven of the 13 patients treated with neostigmine passed stools within 24 h, whereas none of the 11 patients had defecation during placebo infusion. The 11 placebo-treated and the two neostigmine patients who did not pass stools after 24 h of study received neostigmine or placebo, respectively, in a cross-over fashion. Eight of these verum patients passed stools, but none of the placebo-treated patients did. Overall, 79% of the patients passed stools during neostigmine treatment whereas no defecation occurred during placebo infusion. Treatment with neostigmine was tolerated well. In none of the patients did the study medication have to be discontinued for major adverse events; especially, no symptomatic bradycardias occurred. This is in contrast to bolus injections of 2 mg neostigmine in patients with Ogilvie's syndrome, which resulted in symptomatic bradycardia requiring the administration of atropine in two out of 19 patients, while two others vomited [17]. In a minority of our patients, a non-important increase in the production of saliva and sputum was observed. Therefore, the continuous intravenous administration of up to 0.8 mg neostigmine/h to critically ill patients appears to be safe.

While during treatment with neostigmine no complications were observed, three patients (of whom two, after cardiac surgery) developed ischemic complications of the colon 5 days or more after the administration of neostigmine had been stopped. The incidence of ischemic complications of the colon in general ICU patients is not known, but in cardiothoracic patients the in-

cidence is 0.1–0.2 % [5, 18]. In a retrospective analysis in cardiac surgical patients in our hospital, 11 laparotomies for colon ischemia were performed on 3,088 patients (W. Prevoo, data not published). No APACHE II or Goris scores are available for these patients, so a comparison with the patients who received neostigmine cannot be made.

In our study, the patients with colonic ischemia received a significant higher dose of dopamine than the patients without. Also the observation that dopamine dose tended to be higher in those who did not respond to neostigmine than in the responders draws attention to dopamine, especially since no differences were found between responders and non-responders in severity of illness on admission to the ICU, in the degree of organ dysfunction at the time of the study, or in the number of patients receiving morphine prior to the trial. The possible relationship between dopamine and non-responsiveness to neostigmine, and between dopamine and late colonic complications might have several explanations. In the first place, the higher dopamine dose may cause vasoconstriction in the splanchnic vascular bed, leading to ischemia and dysfunction. Secondly, intestinal hypoperfusion occurs in patients with a low systolic blood pressure and/or low cardiac output after cardiac surgery [5]. In these patients, a high incidence of intestinal complications is found, including paralytic ileus [5, 11]. The need for a higher dose of dopamine may reflect a more severe form of shock, i.e. intestinal hypoperfusion. Thirdly, an adverse effect of low-dose dopamine on the motility of the upper gastrointestinal tract is found [19]. A similar effect on the motility of the lower digestive tract might be speculated, especially since dopamine causes muscle relaxation in the colon through β_1 and β_2 receptors [2]. However, no specific dopamine receptors have been found [20]. Finally, the need for high-dose dopamine might be necessary to counteract vasodilatation due to activation of inducible nitric oxide synthetase, causing elevated levels of NO, an inhibitor of intestinal motility [7, 8].

Remarkable is the fact that two of the patients developing late colon ischemia initially passed stools after neostigmine administration. It might be speculated that the muscle activity generated by neostigmine leads to an elevated oxygen consumption in the colon, while this need cannot be met due to an impaired blood flow. The resulting oxygen debt would then lead to gut necrosis later on. However, without treatment, a persistent ileus might lead to further distension of the colon, with progressive impairment of the microcirculation of the colon and ultimately to evident ischemia and perforation as well [10]. At this stage, no conclusions can be drawn regarding risks and benefits of neostigmine on colon (micro-) circulation.

While CIRCI is characterized by non-passage of stools for prolonged periods with normal findings during physical and radiological examination, Ogilvie's syndrome consists of the absence of defecation in combination with colonic distension. It seems probable that Ogilvie's syndrome is preceded by, or is a variant of, CIRCI, and a common pathophysiological mechanism might be presumed. In Ogilvie's syndrome, an imbalance between parasympathetic and sympathetic innervation probably plays an important role [21], as is suggested in paralytic ileus [22]. This neurohumoral dysbalance leads to adrenergic overstimulation and subsequent inhibition of colonic contractions. There are no data indicating an absolute shortage of ACh. The good clinical response to therapy with neostigmine in CIRCI as well as in Ogilvie's syndrome points to a relative deficiency of ACh in both syndromes.

All our patients received SDD [14]. Since SDD therapy is successful in reducing mortality and morbidity only if the non-absorbable antibiotics cover the full length of the gut [23], a good propulsive action is mandatory. Defecation also removes Gram-negative bacteria from the gut and prevents bacterial overgrowth [12, 13]. Both defecation and SDD lower the intestinal endotoxin pool [24]. Furthermore, resolution of a septic state and organ dysfunction has been described after cleansing the bowel [25]. So, passing stools might be beneficial for critically ill patients, whether or not they are treated with SDD.

In conclusion, this study shows that continuous infusion of 0.4–0.8 mg/h of the ACh-ase inhibitor neostigmine promotes defecation in critically ill, ventilated patients with an ileus of the colon, and is well tolerated. Whether defecation results in a better prognosis for the critically ill patient with CIRCI remains to be investigated.

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