

## Case Report

# Neostigmine induced bronchospasm following bradycardia with loss of consciousness: a case report and literature review

Juan Xiong, Aijun Xu

*Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Road, Wuhan 430030, People's Republic of China*

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**Abstract:** Neostigmine is a cholinesterase inhibitor and a primary agent for pharmacologic antagonism for reversal of nondepolarizing muscle relaxants. Due to the parasympathomimetic action, neostigmine can cause nausea, bradycardia, and bronchial constriction. Here we present a patient who developed bronchospasm following bradycardia with loss of consciousness, after the administration of one small dose of neostigmine and atropine. This is the first case to demonstrate such a complicated response to neostigmine. Literature findings suggest neostigmine may induce relatively rare but severe adverse effects during anesthesia emergence, and the newly developed neuromuscular blockade antagonist - sugammadex may be a better choice.

**Keywords:** Neostigmine, adverse effect, muscle relaxants, bradycardia, bronchospasm

### Introduction

Anticholinesterases are the most commonly used agents to reverse residual neuromuscular blockade (NMB) peri-operatively. Here we present a patient who received neostigmine after surgery developed bradycardia, bronchospasm, and unconsciousness. We also review the literature on anticholinesterases and the new NMB reversal agent sugammadex, to make recommendations based on the literature regarding drug safety and effectiveness.

### Case presentation

We present a case of a 34-year-old, 53-kg female (ASA grade I) who came to the Emergency Department with acute abdominal pain for the past 24 hours. Her history and laboratory investigations were unremarkable. The symptoms, laboratory and imaging exams were conducted to diagnose as acute appendicitis. She was planned for emergency laparoscopic appendectomy under general anesthesia.

In the operating room standard monitors with non-invasive blood pressure (NIBP), electrocar-

diography (ECG), and pulse oximetry (SpO<sub>2</sub>) were attached. Her baseline BP was 121/65 mmHg, heart rate (HR) 90 bpm, and SpO<sub>2</sub> 100% on air. The patient was induced with sulfentanyl 30 µg and propofol 100 mg, followed by cisatracurium 8 mg for muscle relaxation. The tracheal intubation was uneventful. Anesthesia was maintained with 2% sevoflurane. Remifentanyl (0.15 µg/kg/min) was administered as analgesic intravenously. Cisatracurium 2 mg was added after surgery started 45 minutes. Sulfentanyl 5 µg was given 30 minutes before the surgery ended for postoperative analgesia. The intraoperative course was unremarkable. A total of 1050 ml lactated Ringer's solution was administered during the 80 minute surgical procedure.

The patient started to spontaneously breathe 2 minutes after the completion of surgery, then neostigmine 1 mg and atropine 0.5 mg were given to counter the residual non-depolarizing motor blockade. The tracheal tube was removed 5 minutes after confirming recovery of consciousness. After extubation, there was no nausea, vomiting, or cough, the SpO<sub>2</sub> was 100%

## Severe adverse effects of neostigmine

on air. Then 3 minutes later, the patient was found unconscious, her vital signs were stable with a BP 120/60 mmHg, pulse rate 70 bpm and SpO<sub>2</sub> 100%. Manual positive pressure mask ventilation with 100% inspired oxygen was immediately started. The end-tidal carbon dioxide (EtCO<sub>2</sub>) was around 25 mmHg. Then 2 minutes later, the patient's HR decreased gradually, and atropine 0.3 mg was given when the HR was 48 bpm, and then the HR elevated back to 57 bpm. However, 1 minute later, the HR was suddenly dropped to 35 bpm with ventricular premature beats seen on ECG monitoring. Chest compression was started and atropine 0.5 mg were administered immediately. The patient's heart rate recovered to sinus rhythm 87 bpm. However, the patient developed expiratory stridor consistent with bronchospasm, and the EtCO<sub>2</sub> lost trace. Bronchospasm was treated by hydrocortisone 100 mg and propofol 50 mg intravenously. Ventilation was improved gradually, and the EtCO<sub>2</sub> increased to 40 mmHg. 30 min later, the patient returned to spontaneous breathing and consciousness. She did not report any pain or discomfort. The patient was transported to the ward later and discharged 3 days after surgery.

### Discussion

In our case, a healthy young woman developed bronchial spasm following loss of consciousness and severe bradycardia after neostigmine and atropine was given. The bradycardia was treated with atropine, and bronchial spasm was controlled with hydrocortisone and propofol effectively. Currently, anticholinesterases are one of the most common reversal agents to prevent residual muscle weakness, i.e. neostigmine [1]. However, the excessive muscarinic effects of neostigmine are of concern, including nausea, bronchial constriction, and bradycardia [2]. The literature was searched for all published case reports of patients who developed major adverse effects following neostigmine administration since 1980 to present on PubMed, and 27 cases were found (**Table 1**).

Neostigmine-induced severe complications are rare, but can be life threatening. The reported cases were seen in all age groups and had a balanced gender distribution. Nearly all these

incidents happened during emergence, when neostigmine was given to antagonize muscle relaxation, except one patient developed cardiac arrest when neostigmine was used to treat bowel obstruction [11]. These severe adverse effects are not predictable and the situation may especially sticky. The cardiovascular system was most frequently involved, and symptoms included malignant arrhythmia, blood pressure fluctuation, asystole, even cardiac arrest. It is noteworthy that patients having a history of cardiovascular disease may have a higher risk of hemodynamic instability. A few patients presented bronchospasm and non-cardiogenic pulmonary edema, most reported cases involved in pediatric patients. It may be related to high airway sensitivity in this special population. Anaphylactic reactions were also reported, and symptoms can vary from rash to anaphylactic shock.

These severe adverse effects of neostigmine lead us to rethink antagonism of muscle relaxants. Sugammadex is a synthetic modified cyclodextrin, has been newly introduced to reverse muscle paralysis [28]. It selectively binds to and encapsulates aminosteroid NM blockers, forming a stable complex which is eliminated renally [29]. Since the reversal is independent of intensity and the duration of NMB prior to sugammadex administration, it is a quite reliable reversal agent. Comparing to neostigmine, sugammadex has a rapid onset of action, it fully reverse NMB in approximately three minutes [30]. Therefore, sugammadex is superior to neostigmine in the 'can't ventilate, can't intubate' situation.

Since it has no receptor effects and no muscarinic effects, use of sugammadex improves patient safety. There is a very low incidence of bradycardia, QT prolongation, and anaphylaxis [29]. For the most up-to-date clinical observations, patients receiving sugammadex had a lower rate of adverse events compared with those given neostigmine during emergence. Risks of bradycardia, postoperative nausea and vomiting (PONV), and overall signs of postoperative residual paralysis were reduced [30-32]. The most common adverse effects of sugammadex are nausea and vomiting. Compared with neostigmine, reversal with sugammadex slightly reduce postoperative nausea or vomiting in patients undergoing laparoscopic

## Severe adverse effects of neostigmine

**Table 1.** Retrospective study of reported cases of neostigmine-related severe adverse effects

No	Author	Age/Sex	History	Symptoms
1	Zhang et al. [3]	12/M	None	Unilateral pulmonary edema
2	Kolker et al. [4]	72/M	HTN	Acute coronary syndrome
3	Choi et al. [5]	73/M	HTN, DM	PVC, skin rashes, hemodynamic instability
4	Cachemaille et al. [6]	68/M	Heart transplantation	Recurrent complete AV block
5	More et al. [7]	9/M	None	Acute pulmonary edema
6	Hermite et al. [8]	12/NA	None	Paradoxical breathing with stridor, hypoxia
7	Tufek et al. [9]	1.6/M	None	Bradycardia, then developed asystolic arrest
8	Yousefshahi et al. [10]	23/F	None	PVC, urticaria
9	Maher et al. [11]	16/F	Cerebral palsy	Cardiac arrest
10	Raiger et al. [12]	45/M	None	Non-cardiogenic pulmonary edema
11	Raiger et al. [12]	6/M	None	Non-cardiogenic pulmonary edema
12	Shields et al. [13]	N/A	Morbid obesity	Persistent heart block, prolonged Q-Tc interval
13	Sawasdiwipachai [14]	1/F	Heart transplantation	Asystole
14	Hazizaj et al. [15]	19/M	Asthma	Bronchospasm, hypotension, tachycardia
15	Zeidan et al. [16]	27/F	Mitral valve prolapse	Ventricular fibrillation
16	Kido et al. [17]	56/M	Heavy smoker	Transient ST segment elevation, variant angina
17	Bjerke et al. [18]	67/M	Heart transplantation	Asystole
18	Seed et al. [19]	64/F	Depression	Rash, bronchospasm, bradycardia, hypotension
19	Pleym et al. [20]	27/F	Long QT syndrome	ventricular fibrillation
20	Kadoya et al. [21]	67/M	WPW syndrome	Rapid atrial fibrillation, hypotension
21	Rodriguez et al. [22]	19/F	HTN	Bradycardia, asystole
22	Beebe et al. [23]	54/M	Heart transplantation	Recurrent asystole
23	Beebe et al. [23]	63/M	Heart transplantation	Asystole
24	Backman et al. [24]	52/M	Heart transplantation	Bradycardia
25	Lonsdale et al. [25]	45/F	Obesity, HTN, DM	Complete AV block
26	Shanka et al. [26]	78/F	HTN	Prolonged bradycardia and hypotension
27	Seidl et al. [27]	51/F	Morbid obesity	Persistent bradycardia and hypotension

Abbreviations: HTN, hypertension; DM, diabetes Mellitus; PVC, premature ventricular contraction; N/A, not available.

surgery and extremity surgery, which has no clinical significance [33, 34]. There is currently no evidence that sugammadex is superior to neostigmine in its postoperative pulmonary complications. Sugammadex administration following laparoscopic sleeve gastrectomy showed no advantage over neostigmine in terms of respiratory complications [35]. There are several reports of sugammadex-induced bronchospasm and pulmonary edema published [36-38]. We also should note that sugammadex has no binding capacity with other muscle relaxants such as succinylcholine, atracurium or cisatracurium.

Our case report and systematic literature review provides important information and is a reference for safe use of NMB reversal agents. As neostigmine administration may cause serious complications such as cardiac arrest and

pulmonary edema. Clinicians especially anesthesiologists should be aware of appropriate use of muscle relaxants and their antagonists.

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The patient consented to the educational publication of this case report and wrote informed consent.

### Disclosure of conflict of interest

None.

### Abbreviations

NMB, neuromuscular blockade; ASA, American Society of Anesthesiologists; NIBP, non-invasive blood pressure; ECG, electrocardiography; SpO<sub>2</sub>, pulse oximetry; HR, heart rate; EtCO<sub>2</sub>,

## Severe adverse effects of neostigmine

End-tidal CO<sub>2</sub>; PACU, Post anesthesia care unit; PONV, postoperative nausea and vomiting.

**Address correspondence to:** Aijun Xu, Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Road, Wuhan 430030, People's Republic of China. E-mail: ajxu@tjh.tjmu.edu.cn

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## Severe adverse effects of neostigmine

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