Severe Bradycardia Induced by Neostigmine Administration in a Patient Receiving Labetalol to Control Intraoperative Hypertension

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Neostigmine is widely used for the reversal of nondepolarizing neuromuscular blocking (NMB) agents. Administration of neostigmine may result in the activation of parasympathetic responses in target organs that may cause a variety of inadvertent reactions, including abdominal pain, excess salivation, vomiting, and bradycardia(1-3). Severe bradycardia induced by neostigmine administration has been reported in patients that received β-adrenergic receptor antagonists, such as propranolol(4), or nadolol(5). In this case report, we described the development of severe bradycardia after the administration of neostigmine in a patient receiving labetalol for the treatment of intraoperative hypertension. The results of this case suggest that labetalol may interact with neostigmine to cause severe bradycardia especially when large doses of neostigmine and labetalol were used. Caution should be used when neostigmine is administered to reverse nondepolarizing NMB agents in patients receiving β-adrenergic antagonists.

Key words: neostigmine, labetalol, bradycardia, general anesthesia

Introduction

Neostigmine, an anticholinesterase agent, is widely used for the reversal of nondepolarizing neuromuscular blocking (NMB) agents. Administration of neostigmine may result in activation of parasympathetic responses in target organs that may cause a variety of inadvertent reactions, including abdominal pain, excess salivation, vomiting, and bradycardia(1-3). Severe bradycardia induced by neostigmine administration has been reported in patients who received β-adrenergic receptor antagonists, such as propranolol(4), or atenolol(5).

Labetalol, a combined α,β-adrenergic receptor antagonist, has been widely used for the treatment of intra-operative hypertension(6). In this case report, we described the development of severe bradycardia after repeated administration of neostigmine in a patient receiving labetalol for the treatment of intraoperative hypertension.

Case Report

A 65-year-old man with rectal carcinoma was scheduled for an operation. He has body weight 60 Kg and height 169 cm. This patient had history of hypertension and diabetic mellitus under regular control using nifedipine and oral hypoglycemia agents. The preoperative laboratory data revealed no significant abnormalities, except for mild renal function impairment with mild elevation of plasma blood urea nitrogen (BUN) 45 mg/dl and creatinine 2.9 mg/dl
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concentrations. Chest x-ray films revealed no evidence of cardiomegaly. EKG showed normal sinus rhythm with a heart rate of 75 beats per minute.

After sedation with 2 mg of midazolam intravenously, general anesthesia was induced using 0.1 mg glycopyrrolate, 100 μg fentanyl, 50 mg 2% xylocaine, and 150 mg propofol intravenously. Tracheal intubation was facilitated with 40 mg of rocuronium intravenously. The surgical procedure was uneventful with estimated blood loss of 400 ml. During the 3-hour operation, two episodes of hypertension (systolic blood pressure more than 150 mmHg and heart rate more than 80 beats per minute) occurred and a total of 10 mg labetalol was used to treat the high blood pressure.

The inhaled anesthetic was discontinued when the operation was finished. To reverse the residual effect of rocuronium, 0.5 mg of glycopyrrolate and 2.5 mg neostigmine were given. Before extubation, a blood pressure of 187/96 mmHg and a heart rate of 100 beats per minute were noted. To treat this pre-extubation hypertensive episode, another intravenous dose of 5 mg labetalol was given. Stable hemodynamic data was observed shortly after extubation. While getting ready for transportation to the postanesthesia care unit (PACU), the patient was closely monitored in the operation room. Unfortunately a moderate amount of blood drained from the surgical drainage tube. An immediate re-exploratory laparotomy was planned to check the intra-abdominal bleeding. Emergent general anesthesia was thus performed using 8% sevoflurane in air (2 L/min) and oxygen (2 L/min) mixture, and endotracheal intubation was facilitated using 25 mg atracurium intravenously. The surgery lasted for an additional 1 hour. After the surgery, the residual effects of the atracurium was reversed using 1 mg atropine and 2.5 mg neostigmine intravenously. After extubation, a blood pressure of 219/103 mmHg and a heart rate of 100 beat per minute were noted. To treat the hypertensive episode, 10 mg of labetalol was given. The blood pressure and heart rate then decreased to around 150/70 mmHg and 70 beat per minute, respectively. The patient was then transferred to the PACU for further observation.

After arriving at the PACU, standard monitors, including non-invasive blood pressure monitor, EKG monitor, and pulse oximetry, were setup and a blood pressure of 150/70 mmHg, heart rate of 50 beats per minute, and SpO₂ of 100% were noted. Due to a gradual decrease in the heart beat, a total dose of atropine 0.8 mg was given to restore the heart rate but in vain. Unfortunately severe sinus bradycardia (heart rate 10-20 beats/min) developed 1 minute after the administration of the atropine. SpO₂ of 100% and drowsy consciousness were found. Two consecutive doses of epinephrine (1 mg each) were give intravenously to treat this episode of severe bradycardia. The respiration was managed with mask ventilation followed by tracheal intubation. After the injection of epinephrine, the heart rate was restored to 120 beats/min and blood pressure was 200/110 mmHg. About 5 minutes after heart rate restoration, the patient regained his consciousness and his hemodynamic condition became stable. The patient was transferred to the intensive care unit (ICU) for further care with a heart rate of 70 beats/min and blood pressure of 160/80 mmHg. No arrhythmia was noted in the ICU and this patient was discharged from the hospital uneventfully 1 week after this incident.

Discussion

Although neostigmine is widely used to reverse the effects of nondepolarizing NMB agents, the use of neostigmine is not without risk. Patients with underlying brady-arrhythmias or those receiving β-adrenergic antagonists may be more susceptible to neostigmine-induced bradycardia⁷.

Neostigmine may induce bradycardia by direct activation of cholinergic receptors within the cardi-
ac parasympathetic pathway. It has a higher sensitivity to muscarinic receptor antagonists than that produced by edrophonium. Asymptomatic heart rate below 60 beats/min may represent an increased vagal tone after administration of neostigmine to reverse the effects of nondepolarizing NMB agents. Careful observation is enough if asymptomatic bradycardia has occurred. Other treatment options include additional administration of atropine which was given with neostigmine.

A bolus intravenous injection of neostigmine at 0.05-0.1 mg/kg was recommended for the reversal of nondepolarizing NMB agents and a total of 5 mg should not be exceeded. Normally atropine is given concomitantly to antagonize the muscarinic effects of neostigmine. Profound bradycardia has been reported after the use of neostigmine, even when concomitantly used with atropine, to reverse neuromuscular blockade in patients taking β-adrenergic antagonist. Sprague reported a profound decrease in heart rate after doses of atropine and neostigmine in patients given β-adrenergic antagonist for supraventricular tachycardia. Dagnino and Prys-Roberts warned of decreased heart rates with neostigmine in patients receiving large doses of β-adrenergic antagonists. β-adrenergic antagonists are widely used to control perioperative hypertension. The properties of all β-adrenergic antagonists and their interaction with anesthetic and anticholinesterase agents are not identical. The main side effect of using β-adrenergic antagonists is bradycardia. Basically, heart rate is determined by an interaction between sympathetic (especially β-adrenergic) and parasympathetic (i.e. vagal) tone. Labetalol is an adrenergic receptor blocking agent possessing both α-1 and β-receptor blocking activity. Its action on β-receptors is four times stronger than that on α-receptors. Following a bolus intravenous injection, the maximum antihypertensive effect occurs within 5-10 minutes, and its duration is 3-6 hours. For patients with decreased hepatic or renal function, the elimination half-life of labetalol is not altered, but the elimination time is reduced in elderly patients. In addition, neostigmine is actively secreted into the tubular lumen. The clearance of neostigmine was reduced in our patient due to his impaired renal function and the plasma concentration of labetalol might have been high due to our patient’s age. Therefore, we think the two agents worked together to induce severe bradycardia.

In summary, this case suggests that labetalol may interact with neostigmine to cause severe bradycardia especially when large doses of neostigmine and labetalol are used. Caution should be used when neostigmine is administered to reverse nondepolarizing NMB agents in patients receiving β-adrenergic antagonist.
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References


術中使用Labetalol控制高血壓的病人，在使用
Neostigmine後產生嚴重心律過慢之病例報告

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Neostigmine被廣泛使用在拮抗非去極化肌肉鬆弛劑，然而因其也作用在副交感神經支配的器官，因此也會產生包括腹痛，嘔吐過多，嘔吐以及心律過慢等副作用。其所造成的嚴重心律過慢已經在包括心
肺移植的病人及使用propranolol或nadolol的病人都被報告過。我們提出一篇病例報告，描述一個因為使用
labetalol控制術中高血壓，同時又因爲外科需要而在拔除氣管內管後又重新置入氣管內管的病人，在重複
neostigmine給予後，產生嚴重心律過慢的病例，以提醒大家neostigmine與較大量labetalol同時使用時，可
能會造成嚴重心律過慢的現象。

關鍵詞：neostigmine，labetalol，心律過慢，全身麻醉

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