Tracheobronchial hypersecretion following neostigmine administration

Seungwoo Rho, M.D.
William H. L. Dornette, M.D., J.D.
John F. Viljoen, M.D.

Division of Anesthesiology

Massive bronchial secretion occurring after the administration of neostigmine bromide (Prostigmin) and atropine to reverse the residual effects of d-tubocurarine is unusual. To our knowledge, there has been no report of this complication, although circulatory arrest of cardiac origin has been reported.[1, 2] During the past 3 years there have been three cases at the Cleveland Clinic Hospital.

Case reports

Case 1. A 56-year-old black man was admitted to the Cleveland Clinic Hospital for bilateral inguinal herniorrhaphy. His medical history was unremarkable. Physical examination revealed a well-nourished man, height 177.8 cm and weight 74 kg, with bilateral inguinal hernias. Laboratory studies disclosed normal values for complete blood cell (CBC) count, blood glucose, serum calcium, and liver function tests; chest roentgenograms were normal. The electrocardiogram (ECG) showed nonspecific changes of S-T segments in I and V6. The patient received premedication at 1 pm, meperidine, 75 mg and atropine, 0.4 mg. On entering the operating room, his blood pressure was 130/75 mm Hg and pulse rate was 80 beats per minute.

Anesthesia was induced at 1:45 pm; thiopental sodium, 300 mg, was administered and endotracheal intubation was performed after he was given 100 mg of succinylcholine chloride. Anesthesia was maintained with halothane-N_2O-O_2, and d-tubocurarine chloride, 12 mg, was administered to obtain muscle relaxation. Respiration was controlled throughout the procedure. Ten minutes after induction of anesthesia there was an episode of mild hypotension, the blood pressure falling to 70/40 mm Hg. This was treated by rapid infusion of 200–300 ml Ringer's lactate solution. The patient was placed in a Trendelenburg position and halothane was discontinued. Thereafter, methoxyflurane, 0.2%–0.3%, was substituted for halothane; the blood pressure remained at approximately 95/65 mm Hg, and pulse rate was 100 beats per minute throughout the 2½-hour operation. Blood loss at operation was about 500 ml, and the patient received a total of 1500 ml of fluid (1000 ml of 5% dextrose in quarter strength saline and 500 ml of Ringer's lactate solution). The chest remained clear.

A mixture of neostigmine, 2.5 mg and atropine, 1.5 mg, was injected to reverse the residual effects of the d-tubocurarine. Ten minutes later the patient did not show any return of normal muscle activity. Clear white frothy secretions then started to pour out of the endotracheal tube. In a period of 3 minutes, 500 ml of fluid accumulated in the suction bottle. Between repeated suctioning maneuvers the patient was ventilated with 100% oxygen.

The blood pressure and pulse remained stable throughout this episode. There were still no spontaneous muscular movements, except occasional slight coughing on suctioning through the endotracheal tube. Because we were not sure whether the cause was bronchial hypersecretion due to a cholinergic crisis or pulmonary edema, atropine, 1.0 mg, was given three times during a period of 10 minutes. In addition, digoxin, 0.5 mg; morphine, 10 mg; furosemide (Lasix), 40 mg; and sodium bicarbonate, 40 mEq, were administered. A central venous catheter was inserted and the initial measurement was 4.0 cm H_2O. The volume of the frothy fluid gradually decreased, blood pressure rose to 200/100 mm Hg and the pulse rate to 170 beats per minute. Arterial blood gas analysis with an FIO_2 of 1.0 revealed a pH of 7.29, pCO_2, 46; pO_2, 250; CO_2 content, 23; and O_2 saturation, 99+%. Controlled ventilation was continued with a volume-cycled machine (Emerson). A chest roentgenogram done during this time showed bilateral diffuse haziness of both lung fields. The ECG suggested left ventricular strain, but when the blood pressure returned to normal it reverted to the preoperative pattern. The plasma cholinesterase activity test by Acholest* (Cholinesterase test-paper) was normal. The vital signs remained stable, the tracheobronchial secretions progressively decreased, and the patient's muscle tone improved. At approximately 10 pm, about 6½ hours after the termination of the anesthetic, the patient was able to move his extremities. The next morning the lung fields were completely clear and the endotracheal tube was removed. There were no residual pulmonary or neurologic complications. A neostigmine sensitivity test was not performed.

Case 2. A 42-year-old white woman was hospitalized at the Cleveland Clinic Hospital for a total hip replacement. She had had a block dissection of neck glands for a mixed-type nodular lymphoma in 1967, which later showed metastasis to the right hip joint. Physical examination showed a well-developed, well-nourished woman; height, 162.6 cm; weight, 59 kg. No nodes were palpable in the neck. The heart and lungs were clear to auscultation and percussion. The CBC, ECG, chest roent-

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genogram, serum calcium, and liver function tests were within normal limits. Premedication included meperidine, 75 mg and atropine, 0.4 mg. When the patient entered the operating room, the blood pressure was 140/90 mm Hg, and the pulse rate was 120 beats per minute. At 12:30 pm, anesthesia was induced with thiopental sodium, 300 mg; endotracheal intubation was accomplished after succinylcholine chloride, 100 mg, was given. Anesthesia was maintained with halothane-N_2O-O_2, and muscle relaxation was obtained with incremental doses of d-tubocurarine (total dose 30 mg). The blood pressure and pulse remained at approximately 120/65 mm Hg and 100 beats per minute respectively throughout the anesthesia. The operation lasted 3¼ hours. Estimated blood loss was about 1500 ml, which was replaced with whole blood. The patient received an additional 1700 ml of fluid (1400 ml of 5% D/¼SS, 100 ml of Ringer's lactate solution, and 200 ml of low molecular weight dextran (Rheomacrodex).

At the end of the operation a mixture of neostigmine, 2.5 mg and atropine, 1.5 mg was injected to reverse the residual effects of d-tubocurarine. After 15 minutes there was no evidence of spontaneous respiratory efforts, and it was noted that secretions began to accumulate in the trachea and bronchi. The patient was taken to the Recovery Room and placed on a pressure-cycled ventilator (Bennett PR II). Approximately 40 minutes after the injection of neostigmine, copious amounts of white frothy secretions poured from the endotracheal tube. Within several minutes 300 ml of secretions were collected in the suction bottle. At this time the patient was quite alert; the blood pressure was 140/90 mm Hg, and the pulse rate was 104 beats per minute. A central venous monitoring line was inserted and the initial measurement was 9 cm H_2O. Intermittent doses of atropine (1.0 mg, total dose 3.0 mg) were injected intravenously during a period of 10 minutes, and the amount of secretions began to decrease. Blood gas studies at this time showed normal findings and the ECG showed no significant changes from the preoperative pattern. The patient was put on an Emerson volume-controlled ventilator. She continued to do well throughout the night and was extubated early the next morning. There were no residual complications.

Case 3. A 66-year-old white man was hospitalized at the Cleveland Clinic Hospital for a right inguinal herniorrhaphy. He had a history of a myocardial infarction in 1955, and since then he had taken digitalis, 0.1 g daily. On physical examination he appeared well developed and well nourished, height, 177.8 kg; weight, 77.2 kg; he had a right inguinal hernia, but was otherwise normal. Laboratory tests showed normal values for CBC, serum sodium, potassium, chlorides, and liver function; blood urea nitrogen (BUN), 20 mg/100 ml; serum creatinine, 1.7 mg/100 ml; the chest roentgenogram was normal. The ECG showed a healed anterior myocardial infarction and first degree atrioventricular block.

At 2 pm, the patient was given meperidine, 75 mg and atropine, 0.4 mg, as preoperative medication. Blood pressure was 120/80 mm Hg, and pulse rate, 100 beats per minute and regular. At 2:45 pm, d-tubocurarine, 3 mg, was administered, following which anesthesia was induced with thiopental sodium, 400 mg. Endotracheal intubation was facilitated by succinylcholine, 100 mg. Muscle relaxation was continued with d-tubocurarine, 27 mg, and anesthesia was maintained with N_2O-O_2 augmented by 0.3% methoxyflurane. The 55-minute intraoperative course was uneventful. The estimated blood loss was approximately 200 ml. The patient received a total of 1100 ml 5% D/¼ SS.

At the end of the operation a mixture of neostigmine, 2.5 mg and atropine, 1.0 mg was injected to reverse the residual

effect of d-tubocurarine. Fifteen minutes later, the patient showed only very weak muscle tone, and copious quantities of white secretions began to well from the endotracheal tube. Vigorous suctioning, together with intermittent positive pressure ventilation with 100% oxygen were carried out. Three hundred milliliters of the secretions were collected in the suction bottle during a 4-minute period. A central venous pressure monitoring line was inserted and the initial measurement was 11.0 cm H_2O. Aminophylline, 500 mg, and furosemide (Lasix), 40 mg, were administered intravenously. As the secretions continued to pour out of the endotracheal catheter, atropine, 1.0 mg, was given and repeated. Within 5 minutes the secretions had diminished. After the patient entered the recovery room he was placed on an Emerson volume-controlled ventilator. Extubation was performed the next morning and there were no residual complications.

Discussion

Normal muscle tone is maintained by the continuous release of acetylcholine. It exerts its effect on the end-plate and is thereafter rapidly hydrolyzed by the acetylcholinesterase which is present in the vicinity of the myoneural junction. D-tubocurarine is a competitive blocking agent and produces its motor paralysis by competing with acetylcholine for motor end-plate receptor sites. Neostigmine inhibits the activity of acetylcholinesterase, thereby allowing a buildup of acetylcholine which overrides the competition for motor end-plate by d-tubocurarine.

Neostigmine inhibits the action of acetylcholinesterase at autonomic effector organs throughout the body. But its muscarinic actions, namely bradycardia and an increase in bronchial secretions are undesirable side effects. Atropine, which blocks the action of acetylcholine,[3] is therefore given either before or at the same time as the neostigmine to prevent these cardiorespiratory side effects. The intravenous dose of neostigmine recommended to reverse the residual action of d-tubocurarine in the average adult is 2.5 mg,[4-6] the recommended corresponding dose of atropine is 1.0 to 1.5 mg, also given intravenously.

In these three cases we are reporting, massive tracheobronchial secretions developed following the administration of neostigmine and atropine in the above mentioned dosage. It seems clear that the dosage of neostigmine was too great, or the dosage of atropine was insufficient, or a combination of these occurred. We believe that these cases represent hyperreactivity to neostigmine. The central venous pressure was well within normal limits in all three patients. Although, as has been previously shown, the central venous pressure may not become elevated immediately following acute left ventricular failure.[7] However, there were no signs of tachycardia, hypotension, gallop rhythm, peripheral vasoconstriction, or cyanosis.

The treatment of this hyperreactivity to neostigmine consists of administration of intravenous atropine in doses of 2 to 4 mg, repeated as required.[8] Atropine effectively antagonizes the actions at muscarinic receptor sites,[3] including the tracheobronchial trees, salivary glands, and central nervous system. This regimen has been adopted for patients with parathion poisoning.

Delayed onset of the tracheobronchial hypersecretion as in one patient (case 2), 40 to 50 minutes, might have

been due to the fact that the duration of action of neostigmine is much longer than that of atropine.

Neostigmine also produces a nicotinic effect. This action is one of stimulation followed by depression of all autonomic ganglia and skeletal muscles. Although both the central and peripheral action of neostigmine may cause respiratory paralysis,[9] we believe that the respiratory paralysis noted in these patients was related to the nicotinic action of neostigmine at the neuromuscular junction level. In these cases, however, the muscular paralysis persisted long after the muscarinic effect had been reversed by atropine. Although atropine is quite effective in treating the muscarinic effects, it is virtually without effect against the peripheral neuromuscular paralysis (nicotinic effect). Pralidoxime chloride (Protopam chloride), a cholinesterase reactivator, can restore a normal response at the skeletal neuromuscular junction.[8] High doses of pralidoxime, however, can in themselves cause neuromuscular blockade.[8] Therefore, the best treatment for neuromuscular blockade probably would be maintenance of artificial respiration until the effect wears off. Digitalis or diuretics or both were administered in cases 1 and 3, since at these stages the possibility of congestive heart failure could not be ruled out. It should be emphasized that these agents do not block the muscarinic effects and do not decrease the tracheobronchial secretions. Measurement of central venous pressure serves as a useful guide in assessing the cardiac condition.

These cases serve to point up the hazards associated with the routine use of any drug. Although the outcome was favorable in each instance, remedial action of an almost heroic nature was required. The importance of making a correct diagnosis promptly, having the proper agents and equipment immediately at hand, and utilizing them without delay, cannot be overemphasized.

Conclusion

Three cases of massive tracheobronchial secretion following the administration of neostigmine to reverse the effects of d-tubocurarine are reported. Large doses of atropine are necessary for the successful treatment of this condition. Complications of this type, although rare, are quite serious. Since total prevention may be impossible, definitive therapy is essential.

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