Case Report

Rare Adverse Drug Reactions to Injection Neostigmine – A Report of Three Cases

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Abstract

Neostigmine Methylsulfate is an anticholinesterase drug administered by anesthesiologists to facilitate speed of recovery from the skeletal muscle effects produced by nondepolarizing neuromuscular blocking drugs. We report three cases posted for elective surgery who underwent uneventful surgeries following thorough preoperative checkup, and developed reactions on receiving Injection Neostigmine in the form of ventricular tachycardia and ventricular fibrillation. All three patients survived and were later discharged due to timely diagnosis and prompt management.

Keywords: Neostigmine Methylsulphate, Acetylcholinesterase, Ventricular Tachycardia, Ventricular Fibrillation

INTRODUCTION

Neostigmine is a synthetic quaternary ammonium parasympathomimetic agent. It is an anticholinesterase used to reverse neuromuscular blockade. Anticholinesterases exert their effect primarily by inhibiting acetylcholinesterase and thus increasing the concentration of acetylcholine at the motor end plate. Neostigmine transfers a carbamate group to acetylcholinesterase and at the esteratic site covalent bond is formed. In addition, anticholinesterases anticholinesterase may increase the release of acetylcholine from presynaptic nerve terminals.[1,2] As there is increase in acetylcholine which is caused by Cholinesterase inhibitors, it affects more than the nicotinic receptors of skeletal muscle. Predominant Muscarinic effect on the heart is a vagal like bradycardia that can progress to sinus arrest. Other muscarinic side-effects include dysrhythmias, bronchospasm, bronchial secretions, intestinal spasm, increased salivation, increased bladder tone and pupillary constriction.[3]

CASE REPORT

We report 3 cases posted for elective surgery after thorough preoperative checkup who suffered from ventricular tachycardia and ventricular fibrillation leading to cardiac arrest during reversal of residual effect of non-depolarising muscle relaxant with Neostigmine, on the same day and in the same institute, requiring critical care management.

Case Number 1

A 60 years old male patient was admitted for recurrence of verrucous carcinoma of the hard palate and posted for excision of the carcinoma under general anaesthesia. He was previously operated thrice for the same under general anaesthesia and all the three surgeries had been uneventful. Preoperative work-up was normal and patient underwent routine induction of anaesthesia. The intraoperative course was uneventful. For reversal of muscle relaxation, patient was given Injection Neostigmine 2.5 mg and Injection Glycopyrrolate 0.4 mg slowly IV. Patient was then extubated and oxygenated on Ventimask. Vitals of the patient were stable during extubation. The patient developed sudden tachycardia progressing to SVT on ECG with pulse rate 160-180/min.

100% O_2 was given using Bainscircuit with mask, followed by carotid massage. Injection Amiodarone 150 mg IV bolus given slowly. The ECG showed SVT progressing to ventricular fibrillation. CPR was immediately instituted. 2 DC shocks of 200 J were given stat. ECG showed sinus rhythm. The blood pressure then dropped suddenly to 70 mmHg systolic. Injection Dopamine drip (800 mg in 500 ml D5) was started @ 24µdrops/min. Patient was re-intubated with an endotracheal tube and 100% O_2 was

given. Patients heart rate and blood pressure stabilized. ECG started showing occasional ectopics. Injection Amiodarone 900 mg in 500 cc of 5% was started @ 30 μdrops/min. Patient was then shifted to CCU in intubated and paralyzed condition and put on CMVmode of ventilation. Patient was gradually weaned off the ventilator. Amiodarone and Dopamine drips were tapered and stopped. Vitals of the patient were maintained, ECG was normal. Patient was then extubated and transferred to ward.

Case Number 2

A 35 years old male patient was admitted with diagnosis of hereditary spherocytosis with splenomegaly with cholelithiasis. He was posted for splenectomy with cholecystectomy. On physical examination, patient was having icterus and pallor. The serum indirect bilirubin levels were elevated (Indirect 4.4 mg/dl, Direct 0.1 mg/dl). USG Abdomen revealed gross splenomegaly and cholelithiasis. Intraoperative course of the patient was uneventful. For reversal, Injection Neostigmine 2.5 mg + Injection Glycopyrolate 0.4 mg diluted to 20 cc with normal saline was given slowly IV. After injecting 5 ml (0.625 mg of Neostigmine) patient developed ventricular tachycardia and sudden rise in BP followed byhypotension. Reversal was stopped and resuscitation was started immediately. Injection Lignocaine 60 mg was given stat. There was no change in rhythm. 1st D.C. shock of 360 J was given → Injection Adrenaline 1 mg IV given stat →2nd D.C. Shock of 360 J given→ Injection Adrenaline 1 mg IV repeated → Total 8 D.C. Shocks – 360J given. Call was sent for cardiologist. Injection Amiodarone 150 mg IV bolus given slowly. ECG – sinus rhythm returned. BP was still 60 mm Hg systolic. Injection Dopamine 800 mg + Injection Adrenaline 2 mg in 500 ml normal saline drip started @ 80 ml/hr Injection Amiodarone 300 mg in 250cc NS drip started @ 20 ml/hr. Blood was sent for serum electrolytes. Sr.Na^+ – 138 mEq/lit, Sr.K^+ – 3.3 mEq/litre. Urine output was 250 ml. Patients spontaneous activity returned, started responding to verbal commands, opening eyes, and moving extremities. Patient was then re-paralysed with Inj. Atracurium 25 mg and ventilated with Bains circuit with 100%O_2. Patient was observed in O.T. for 45 min. Pulse rate – 134/minutes regular rhythm, BP – 100 mmHg systolic. Patient was then shifted to CCU in intubated and paralyzed condition and put on CMV mode of ventilation with 100%FiO_2. Patient was monitored in the CCU→one episode of hypotension observed. BP – 74 mm Hg systolic. 1pint Blood given,1 pint colloid (hydroxyethylstarch) started. Dopamine + Adrenaline drip @80 ml/hr and Amiodarone drip @25 ml/hr continued. Patient suffered from 4 episodes of ventricular tachycardia requiring defibrillation between 2:45 a.m. to 6:45 a.m. Next day, vitals were stable, weaning from Dopamine and Amiodarone drips started. Weaning from ventilator started. Troponin T done as advised by cardiologist was negative. No further irregular rhythm observed. Both drips were tapered and stopped. Patient was extubated two days later after gradual weaning from the ventilator and then transferred to ward after 4 days stay in CCU for monitoring and observation.

Case Number 3

A 75 yrs old female patient diagnosed with cholelitiasis was posted for open cholecystectomy. Intraoperative course was uneventful. For reversal of muscle relaxation, Injection Neostigmine 2.5 mg + Injection Glycopyrrolate 0.4 mg diluted to 20cc with normal saline was given slowly IV. After good respiratory efforts returned, patient was obeying commands, opening eyes, reflexes present, head lift present. Thorough oral suctioning was done and the patient was extubated. 5 minutes after extubation patient had an episode of sudden bradycardia and hypotension P – 54-55/min. BP – 90 mmHg systolic. Injection Atropine 0.6 mg iv given stat IV, colloid(hydroxyethylstarch) started. P – 90/min, BP – 120 mmHg systolic, ECG showed ST elevation. Patient was observed for 2 hrs in O.T.P – 70-80/min, BP – 110/70 mmHg, SpO_2 – 96% on ventimask ECG – changes reverted to Normal, U/O – 150 ml. Patient wasshifted to ward for further monitoring and management. At 4:35 a.m.patient developed sudden breathlessness and was shifted to MICU. ECG showed T wave inversion in leads I, aVl and V_{4-6}. Troponin T test – positive, CPK – MB – 11.8 ng/ml (Normal: 0-5 ng/ml). Impression given by cardiologist was Non-ST segment elevation myocardial infarction (Subendocardial infarct). 2D-ECHO was essentially normal. Patient was observed and monitored in MICU. She was at a later date diagnosed to have developed drug induced chemical myocarditis.

DISCUSSION

Neostigmine Methylsulfate is an anticholinesterase agent used to reverse the residual muscle relaxation following administration of non depolarizing muscle relaxants during anesthesia. The known cardiovascular adverse effects includes syncope and hypotension, cardiac arrhythmias (including bradycardia, tachycardia, A-V block and nodal rhythm) & as cardiac arrest. In all the three cases we have reported, the patients posted for elective surgery underwent uneventful operations following thorough preoperative checkup but developed adverse reactions on receiving Injection Neostigmine in the form of ventricular tachycardia and cardiac arrest on the same day. Two of these patients were shifted to CCU for ventilator and critical care management and one patient was treated and shifted to ward and then to MICU for further management. All these 3 patients were saved by timely diagnosis and intervention

and were subsequently discharged. After this incident, a meeting took place between Anesthesiologists, Physicians and Pharmacologists. ADR was submitted following which routine procedure was followed, viz stop use, withdrawal of stocks and dissemination of information to all other Government centers in the state of Maharashtra and also to DMER, DEHS, ESIS, Assistant Director of Rate Contract Cell, DMER, Mumbai. Then said defective batch of Injection Neostigmine was sent to FDA for analysis on 25/12/2007. Their report stated the batch of Injection Neostigmine was substandard.

Bradycardia leading to sinus arrest is a known complication of Neostigmine. In 2005, Zeidan A and Baraka reported a case of ventricular fibrillation following atropine-neostigmine mixture in a patient with undiagnosed mitral valve prolapsed.[4] In 1995, J Rodríguez, J Cortiñas et al reported bradycardia and asystole following atropine-neostigmine administration after caesarean section in a parturient receiving methyldopa for pregnancy-induced hypertension attribute this adverse reaction to the treatment of pregnancy-induced hypertension with methyldopa, perhaps facilitated by other drugs employed.[5] In 1956, Lawson described successful resuscitation of a patient with sudden cardiac arrest following administration of Neostigmine.[6] In 2004, Liaquat Ali, Mahmood Akhtar described a case of cardiac arrest following the administration of neostigmine and atropine which was detected in time and managed successfully.[7]

Thus, the three case reports presented emphasize the need on the part of anesthesiologists to be vigilant while using drugs, promptness to manage any undue complications, and communication between them so as to prevent potentially fatal complications resulting from the use of substandard drugs.

REFERENCES

1. Stoelting, R. K, Hillier, SC. Pharmacology and physiology in anesthetic practice. Lippincott Williams & Wilkins. 3rd ed. Chapter 9. 2012, Page No:224-236.
2. Ronald D. Miller. Millers Anesthesia. 7th ed. Chapter 29, 2010, Page No: 859-911.
3. Morgan, G. Edward, et al. Clinical anesthesiology. New York, NY: Lange Medical Books/McGraw-Hill. 2006.
4. Zeidan A, Baraka A. Ventricular fibrillation following atropine-neostigmine mixture in a patient with undiagnosed mitral valve prolapsed. *Anaesthesia*. 2005;60(7):724-725.
5. J. Rodríguez, J. Cortiñas, et al. Bradycardia and asystole following atropine-neostigmine administration after caesarean section in a parturient receiving methyldopa for pregnancy-induced hypertension. *International Journal of Obstetric Anesthesia*. 1995;4(1):55-57.
6. Lawson JI. Cardiac arrest following the administration of neostigmine. *British Journal of Anaesthesia*. 1956;28(7):336-337.
7. Liaquat Ali, Mahmood Akhtar. Cardiac arrest following the neuromuscular blockade reversal with Neostigmine and Atropine. *Professional Med J*. 2004;11(2):228-31.

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