CASE REPORT PROF-773

CARDIAC ARREST FOLLOWING THE NEUROMUSCULAR BLOCKADE REVERSAL WITH NEOSTIGMINE AND ATROPINE

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ABSTRACT... Neostigmine and atropine are routinely used during anaesthesia for the reversal of neuromuscular blockade. Administration of this mixture is occasionally associated with various cardiac arrhythmias and rarely cardiac arrest. A case of cardiac arrest following the administration of neostigmine and atropine is described, which was detected in time and managed successfully.

Key Words: Neostigmine, Neostigmine – Atropine, Neuromuscular blockade reversal, Cardiac arrest.

INTRODUCTION

Non-depolarizing muscle relaxants are used in almost all the operations longer than a few minutes These relaxants also called as competitive antagonists, compete with acetylcoholine (ACH), reversibly binding with post-synaptic membrane receptors at the neuromuscular junctions. Ach is not allowed to act on these receptors, there is no end plate depolarization and muscle relaxation occurs[1]. Neostigmine causes accumulation blockade. Cardiovascular effects of neostigmine are due to the accumulation of Ach at the muscarinic receptors and include severe bradycardia, hypotension, various cardiac arrhythmias and cardiac arrest.

CASE REPORT

A 26-years old multigravida (G_5 P_4) presented for emergency caesarean section at the Armed Forces Hospital, Najran, Kingdom of Saudi Arabia. She weighed 64 kg, was not empty stomach and no investigations were available. Her blood pressure was normal and clinical examination did not reveal any abnormality. This was her first operation under general anaesthesia.

A wedge was placed under the right hip to prevent aortocaval compression. After pre-oxygenation with 100% oxygen for 3 minutes, rapid sequence induction was done with thiopentone sodium 250 mg and succinylcholine chloride 100 mg, and cuffed endotracheal tube was passed. Capnography and auscultation of both sides of the chest were used to confirm tube placement and bilateral air entry. An anaesthesia was maintained with oxygen and nitrous oxide 50% each, with 0.5 MAC (minimal alveolar concentration) isoflurane. 20 mg of atracurium

besylate was used as muscle relaxant. Pethidine 50 mg was given after delivery of the baby. The baby had an Apgar score of 8/10 at one minute and 10/10 at 5 minutes. Monitoring included non-invasive blood pressure every 5 minutes, and continuous ECG and pulse oximetry. The patient remained stable throughout the operation.

At the end of the operation, residual muscle paralysis was reversed with neostigmine 2.5 mg and atropine 1.2 mg, given slowly over 2 minutes. Immediately after the neostigmine atropine mixture had been given, patient developed bradycardia with a heart rate of 30-35 per minute. Patient was receiving 100% oxygen and was given one mg atropine IV (intravenously). In the meantime patient went into asystole. Immediately, external cardiac massage was started and adrenaline one mg IV was given.

Now the patient developed ventricular fibrillation. 200 joules were given in succession and she got defibrillated at the second attempt. Within two minutes of asystole, patient was having sinus rhythm with heart rate of 102 – 108 per minute, slight ST-elevation and a blood pressure of 85/50 mm of Hg. She was kept intubated. Within 30 minutes, tachycardia and ST – elevation got settled and blood pressure became normal (125/84 mm Hg). 50 mg pethidine IV was given during this period. Patient was not fully conscious and was having laboured breathing with an oxygen saturation of 88% while receiving 100% oxygen.

Clinically she was found having pulmonary oedema, which was later confirmed by X – ray chest, Arterial blood gases (ABGs) done at this stage showed a PaO_2 of 212 mm Hg on 100% oxygen, $PaCO_2$ 42 mm Hg, HCO_3 20 mEq/L, pH 7.28 and base excess of – 10 mEq/L., She was put on the ventilator on SIMV (synchronized intermittent mandatory ventilation) mode with PEEP (positive end expiratory pressure) of 5 – 7.5 cm of water. Lasix 40 mg IV was given 8 hourly. Suction from the endotracheal tube was done on as required basis. She was kept sedated with morphine 2.5 – 5 mg/hour and midazolam 2.5 – 5 mg/hour. Intraoperative specimens of blood complete picture and blood chemistry were sent and were found to be within normal limits. Her pulmonary oedema settled within 24 hours and she was weaned off easily.

Her cardiac enzymes were raised but became normal at 72 hours (Table-1). Patient had no recall of the incidence. She was informed about the event and was given a detailed written account of the whole incidence to inform her future anaesthetist, in case she needs a general anaesthesia. She was discharged from the hospital on 10th postoperative day without any complaints. She was asked to report after one month and was found to be perfectly all right.

Table -I Cardiac enzyme following asystole

Enzyme	at 9 hours	at 72 hours	normal values
C P K	459 U/L	126 U/L	30 - 135 U/L
CK-MB	221 U/L	11 U/L	0 - 16 U/L
Enzyme	**AT 15 hours**	**at 72 hours**	**normal values**
LDH	910 U/L	432 U/L	313 - 618 U/L

CPK - Creatine phosphokinase.
CK-MB= Creatine Kinase, MB fraction, LDH = Lactate dehydrogenase, U/L Unit per litre.

DISCUSSION

Ach is the neurotransmitter at the neuromuscular junctions. It is synthesized in the nerve terminals from acetylcoenzyme A and choline by the enzyme choline acetyltransferase (formally known as choline accetylase) and transferred into the synaptic vesicles of about 50 nm diameter, which are stored as multimolecular packages or quanta. When a nerve impulse reaches a nerve terminal, quanta of Ach are released. Entry of Ca^{++} ions into the nerve terminal is necessary part of this process[2]. After release, Ach combines with nicotinic receptors at the post-synaptic membrane. This interaction causes a decrease in the transmembrane potential from -90

mv to -50 mv. This in turn generates an action potential, which is propagated along the sarcolemma, resulting in muscle contraction[3]. Small quanta of Ach continue to be released spontaneously from the nerve terminals, causing miniature end plate potentials (MEPPs) of – 1 mv to – 1.5 mv, but these are not sufficient to generate an action potential and cause muscle contraction . Released Ach is broken down within 15 m sec into acetic acid and choline by the enzyme cholinesterase, present in the synaptic cleft and folds of post-synaptic membrane. Non-depolarizing muscle relaxants, also called as the competitive antagonists, reversibly bind with the post-synaptic receptors and do not allow the Ach to act. There is no end-plate depolarization and muscle relaxation occurs.

Neostigmine, an anticholinesterase, inhibits the enzyme cholinesterase, resulting in the accumulation of Ach at the cholinergic receptors. With time, concentration of muscle relaxants at the neuromuscular junctions decreases due to hydrolysis and redistribution, and accumulated Ach competes with the relaxants to reverse the residual neuromuscular blockade[4].

Cardiovascular effects of neostigmine depend on the relative stimulation of muscarinic and nicotinic receptors. Peripheral accumulation of the Ach may cause profound bradycardia due to vagal stimulation. Vasodilatation and hypotension may occur.

For the reversal of neuromuscular blockade, neostigmine is given in the dose of 40 – 45 μgm/kg combined with atropine 15 – 20 μgm/kg, to prevent its muscarinic effects. Arrhythmias and cardiac arrest have been reported following the administration of neostigmine and atropine[5,6]. Injection of neostigmine-atropine mixture impairs cardiac baro reflex sensitivity and high frequency component of heart rate variability in the early postoperative period, thus leading to increased cardiac arrhythmias. Indices of parasympathetic modulation of heart rate are impaired for at least 120 minutes after the administration of neostigmine and atropine[7]. The arrhythmias common to the combination or to each individual drug are, Wenckebach phenomenon, premature atrial contractions, junctional rhythms, atrioventricular dissociation, premature ventricular contractions and bigeminy [8,9,10,11].

Occasionally, when the muscarinic effects are blocked by atropine, or when large doses are used, the blood pressure and heart rate may rise due to stimulation of autonomic ganglia and release of adrenaline from the adrenal medulla (nicotinic effect).

At one time the teaching was to give atropine first, wait for an increase in the heart rate and then give neostigmine. The tachycardia in this case was almost twice than when both the drugs were given together. Atropine, when given with neostigmine, has a biphasic action, there is an initial tachycardia followed by bradycardia. Present teaching is to give neostigmine and atropine together, as vagolytic effects of atropine precede the muscarinic effects of neostigmine by 1 – 2 minutes [12]. Atropine in the dose of 20 μgm/kg produces maximal vagal inhibition, and is the recommended dose when given with neostigmine[13]. When given in combination, smaller doses of atropine produce unacceptable decrease in heart rate whereas larger doses are associated with greater incidence of dysrrhythmias[14]. Dangerous bradycardia may occur when neostigmine is used in patients taking digitalis. Patients with first degree heart block may progress to greater degree of block with neostigmine and it must be used with caution in patients with conduction defects[15]. Hypoxia and hypercarbia increase the incidence of dysrrhythmias in patients given neostigmine-atropine mixture[16]. Incidence of cardiac dysrrhythmias following neostigmine is also higher in elderly patients with cardiovascular disease[17].

CONCLUSION

Critical events due to drugs have a low prevalence during anaesthesia, but do occur. Anaesthetist must be familiar with the pharmacology and management of side effects, of the drugs they are using. Adequate monitoring and constant vigilance are required during the administration of any anaesthetic, for prompt

diagnosis and management of such events. Any delay in the diagnosis and treatment may be associated with a poor outcome and may make the anaesthetist liable to professional negligence.

Slow administration of neostigmine –atropine mixture (over 2-5 minutes), avoidance of hypoxia and hypercarbia at the time of reversal and extra vigilance when using this mixture in patients with heart blocks, those taking digitalis and in the elderly are suggested.

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