Unexpected prolonged neuromuscular block after a single intubating dose of mivacurium: a case report

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Abstract - A 22-year-old woman admitted for tonsillectomy developed prolonged neuromuscular block after a single intubating dose of mivacurium. Laboratory testing showed a pseudocholinesterase phenotype of E1a E1j and a dibucaine number of 46%, associated with decreased plasma pseudocholinesterase activity. Current diagnosis and management are discussed.

Keywords - prolonged neuromuscular blocking, pseudocholinesterase deficiency, mivacurium

Introduction
Mivacurium is a nondepolarizing neuromuscular blocking agent (NMBA) that has a short duration of action. The administration of 2x ED95 mivacurium (intubating dose) results in a neuromuscular block (NMB) for 15-20 minutes and spontaneous recovery is 95% complete within approximately 25 to 30 minutes. Mivacurium is metabolized and inactivated in plasma by hydrolysis of the enzyme cholinesterase-II (CHE-II) or pseudocholinesterase (PCE), which is synthesized in the liver.

The duration of an NMB with mivacurium may be prolonged in deficiency or reduced activity of PCE. Several cases of prolonged paralysis after inducing NMB with mivacurium in patients with impaired activity of plasma PCE have been reported [1,2]. Here, a case is reported in which a patient had an unexpectedly prolonged NMB after a single dose of mivacurium. In addition, an overview is given of the genotypes discovered so far which lead to reduced PCE activity.

Case report
A 22-year-old woman, weight 66 kg and height 1.75m, presented for tonsillectomy. Her medical history revealed two uncomplicated ear operations 7 and 12 years earlier. Her personal and family history was not suggestive of anaesthetic problems. Premedication consisted of oral midazolam 7.5 mg. Standard monitoring, including non-invasive arterial pressure, oxygen saturation and electrocardiography was performed. Anaesthesia was induced with propofol 120 mg, sufentanil 15 μg and mivacurium 15 mg intravenously, followed by tracheal intubation. The lungs were ventilated with a mixture of oxygen and air at a ratio of 2:3. Anaesthesia was maintained with sevoflurane. The duration of anaesthesia was 30 minutes and the surgical procedure was uneventful. However, the patient’s recovery from anaesthesia was complicated by prolonged NMB; there were no signs of spontaneous respiration. Neuromuscular monitoring (NMT Datex-Ohmeda) showed a residual neuromuscular block. Therefore, anaesthesia was continued with midazolam only (0.01 mg/kg/h) for sedation and the patient was transferred to the Intensive Care Unit for mechanical ventilation and sedation.

Physical examination and laboratory findings including renal function, hepatic function and blood counts showed no abnormalities. Midazolam at 0.06 mg/kg/h and fentanyl at 0.001 mg/kg/h were given intravenously. Four hours after the single intubating dose of mivacurium spontaneous muscle activity was observed and the midazolam and fentanyl were discontinued. After five hours the trachea could be extubated. Further recovery was uneventful and the patient was fully informed of her complicated recovery from anaesthesia.

Further diagnostic investigations revealed a negative pregnancy test, and TSH and freeT4 values were normal. PCE count was 1360 U/L (normal range: 4000-10000 U/L), and the dibucaine number was 46% (normal >70%). Genotyping of the PCE showed E1a E1j, which is considered a rare genotype.

Discussion
In this case report we described prolonged NMB after a single intubating dose of mivacurium due to a reduced activity of PCE. This condition is most often recognized if NMB unexpectedly persists for a prolonged period of time following administration of standard doses of mivacurium or succinylcholine, a depolarizing NMB. A reduction in activity of PCE results in increased potency of mivacurium or succinylcholine, decreased clearance and a significantly longer elimination half-life.

Causes
The causes of reduced catalytic activity of PCE can be physiological, acquired or inherited. Prolonged mivacurium-induced NMB is seen in pregnancy, liver failure and hypothyroidism. In pregnancy, the PCE activity can be decreased by up to 30% of pre-pregnant levels from 10 weeks gestation until term. The PCE levels will return to normal about 6 weeks later. Thirty percent of functional reduction will not always lead to prolonged NMB on the use of mivacurium [3]. Some chemotherapeutics, such as...
cyclophosphamide, can inhibit PCE and can lead to prolonged NMB when given prior to surgery [4]. Furthermore, in patients with hypothyroidism, a decrease in plasma PCE activity was found on comparison with euthyroid controls [5].

In addition to acquired abnormalities or variants, differences in genotype can be responsible for the reduction of PCE function. PCE is determined by two autosomal genes. These autosomal allelic genes are located at locus E1 and E2, and only the genes located on E1 code for the synthesis of variants of pseudocholinesterase. Up to 1975, four different alleles had been identified: Eu1 (usual), Ea1 (atypical or dibucaine resistant), Ef1 (fluoride resistant), and Es1 (silent). The silent allele does not produce any cholinesterase activity and has been found to exist in two different forms [8]. In 1975, including these four alleles, 11 different genotypes had been identified.

From 1975 genetic evaluation enabled the recognition of two new alleles - Ej1 and E1k - in family pedigrees. One study found that the Ej1 allele results in a decrease of circulating E1u molecules and thereby reduces the PCE activity by 65 to 70% [7]. E1k was found to have a frequency of 19.6% in the normal population with a homozygote genotype E1kE1k with a frequency of 3.8% [8-10]. Now, thirteen different genotypes of the PCE gene have been identified [11] and at least 60 genetic variations of the PCE gene have been described. The homozygote Eu1 genotype, indicating no prolongation of NMB after mivacurium use, has the highest incidence in healthy humans. Of the different genotypes, the homozygote silent variant is of special clinical significance because of the prolonged NMB.

In our case, genotyping of the pseudocholinesterase showed E1aE1j. The incidence of this particular phenotype is unknown. Garry et al report a frequency of 11.4% in the pedigree of a single family [9]. The family history of the patient in this case was negative, but since she has a twin sister genetic evaluation is strongly recommended.

The direct PCE activity helps to identify deficiencies, but there is a wide range in normal values in humans. Therefore, the dibucaine number (DN) can be of use. Dibucaine is an agent that inhibits normal plasma cholinesterase activity by 70%. The dibucaine number applies to the percentage inhibition of the activity of cholinesterase in the presence of dibucaine. Hereby, the DN reflects the ability to metabolize mivacurium and not the quantity of circulating enzyme in the plasma [12]. In our patient, the DN of 46% confirmed the diagnosis of insufficient PCE activity.

**Neuromuscular monitoring**

Neuromuscular blockade after administration of muscle relaxants can be quantitatively monitored by using a device that stimulates the ulnar nerve. By measuring the response of the consecutive muscle, the level of neuromuscular block can be obtained. The train-of-four mode (TOF) is a method in which four consecutive stimuli are delivered to measure residual neuromuscular block [13]. In this case, at the end of the surgical procedure the TOF was 0 (no response) and the patient was transported to the Intensive Care Unit. Unfortunately, no neuromuscular monitoring was available on the ICU. However, after this particular case, the protocol has been changed and in the future neuromuscular monitoring will be applied on the Intensive Care Unit if needed.

**Treatment**

Prolonged NMB due to reduced PCE function is treated by mechanical ventilation, comfort care and expectant management. Neuromuscular monitoring is recommended. Intravenous injection of cholinesterase increases the metabolism of mivacurium, which leads to shorter mivacurium action and thus shorter neuromuscular block [14]. The clinical use of this agent is limited by its availability. Another treatment is the administration of fresh frozen plasma (FFP) in order to enlarge the amount of normal PCE and to hydrolyse the mivacurium. However, side effects are numerous and can be dangerous. The transfusion of plasma can cause transmission of infectious disease, anaphylactic reactions, and pulmonary oedema. Furthermore, the activity of PCE in the FFP is not known.

**Recommendations**

Education is essential in patients with reduced activity of PCE to avoid the use of mivacurium or succinylcholine. Patients with known PCE deficiency may wear a medic-alert bracelet that will notify healthcare workers of the increased risk from administration of mivacurium or succinylcholine. These patients also should notify their family who may be at risk of carrying one or more abnormal pseudocholinesterase gene alleles.

In patients with PCE deficiency the use of a steroidal NMB such as rocuronium or vecuronium is recommended to induce NMB. These drugs are not dependent on PCE for metabolism and more importantly, these NMBA can be safely and efficiently reversed by sugammadex, the first selective relaxant binding agent [15].

In conclusion, prolonged NMB after administration of mivacurium mostly takes no more than a few hours and is not associated with a worse outcome. Therefore, we strongly recommend supportive treatment: mechanical ventilation and sedation, diagnostic investigations regarding the cause of prolonged NMB, monitoring of NMB and patient education to avoid the increased risk of prolonged NMB caused by these agents.
References