Pharmacogenetic Alteration of Mivacurium Metabolism Causing Prolonged Neuromuscular Blockade

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INTRODUCTION

Neuromuscular blocking drugs are used during anesthesia to facilitate endotracheal intubation and mechanical ventilation. Succinylcholine, a depolarizing neuromuscular blocking agent, is often chosen for intubation because of its rapid onset and short duration of action. However, the use of succinylcholine is associated with postoperative muscle pain, hyperkalemia, increased intraocular, and intragastric pressure. Mivacurium, a rapid acting nondepolarizing neuromuscular blocking agent, has recently become available in Trinidad. It has a pharmacokinetic profile similar to succinylcholine, but is devoid of the adverse effects listed above. Since it is hydrolyzed by pseudocholinesterases, the duration of action is prolonged in patients with low pseudocholinesterase activity. We report here on a case of prolonged neuromuscular blockade in a patient who received mivacurium and enflurane anesthesia.

CASE

A 28 year-old female patient (weight 43 kg, height 135 cm) of Asian Indian descent was brought to the Same Day Surgery Department for reconstruction of Pes Planus of the right foot. She was ASA grade 1 with no systemic disorders as classified by the American Society of Anesthesiologists. Neither she nor her family had any previous anesthetic history. Contributory medical history revealed allergic reactions to shellfish. Pre-operative blood investigations of ESR, complete blood count, liver, and kidney function tests were within normal ranges.

Prior to surgery, she was extremely anxious and apprehensive and was administered midazolam 5 mg IV. After pre-oxygenation, anesthesia was induced with fentanyl 25 mg and propofol 70 mg. She received a total dose of 12 mg mivacurium of which 1 mg was a priming dose. The patient was maintained on oxygen, nitrous oxide, and enflurane until relaxation was achieved for intubation, and then put on intermittent positive pressure ventilation.

Within 2 to 3 minutes after induction, several wheals appeared along the forearm that was injected. As this was attributed to histamine release from mivacurium, chlorpheniramine 10 mg IV was administered following which the reaction subsided. There was no change in arterial blood pressure or pulse rate to indicate any systemic release of histamine. The patient received ketorolac 30 mg IV for analgesic and anti-inflammatory effects.

Fifteen minutes after induction, while drapes were being applied and the patient was being appropriately positioned, she appeared to have moved. A peripheral nerve stimulator was not available to assess the degree of neuromuscular blockade, therefore, she received a supplemental dose of mivacurium 4 mg IV. Surgery lasted for an hour and a quarter without any apparent need for further mivacurium. Pulse oximetry and capnography values remained within acceptable limits. The patient regained spontaneous ventilation about 5 minutes after surgery ended without any delay in respiratory movements and, therefore, reversal agents were not needed.

Post-operative nausea and vomiting were treated with dimenhydrinate 50 mg IV. The patient awoke in the recovery room and was comfortable, since the wound had been infiltrated with 0.25% bupivacaine mixed with 2% plain lidocaine. On full orientation approximately 25 minutes later she was transferred to the surgical ward.

During the entire period of surgery, supplemental doses of mivacurium were not required alerting the anesthetic team to its unexpected prolonged duration of action (normal duration 14–16 minutes). A blood sample was therefore collected the following day and serum separated for estimation of the dibucaine number and cholinesterase.

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plasma pseudocholinesterase activity. Analysis of the dibucaine number and cholinesterase levels employed UV/VIS spectrometry (HP Model 8452 A) at 240 nm and 410 nm, respectively.

The dibucaine number is calculated by determining the differential percentage inhibition of cholinesterase in serum diluted 1:100 using benzoylcholine as a substrate. The rate of hydrolysis of benzoylcholine was determined at 240 nm in the presence and absence of 10^(-3) M dibucaine. The patient’s dibucaine number was estimated to be 53.

Cholinesterase assay was based on the modified Ellman reaction using propionylthiocholine iodide (PCTI) as the substrate and 5,5'-disulfobis(2-nitrobenzoic acid) which couples with the hydrolytic product of PCTI at 38°C; the rate of the formation of the coloured product was followed at 410 nm spectrophotometrically. Estimation was done in triplicate and the mean cholinesterase value was 0.93 U/mL.

**DISCUSSION**

Mivacurium is a non-depolarizing, neuromuscular, blocking benzylisoquinolinium compound, but like succinylcholine it is rapidly degraded by plasma pseudocholinesterase. It obeys first-order kinetics and its quick hydrolysis permits a short duration of action of 14-16 mins. Hydrolysis of mivacurium increases as substrate concentration increases contributing to the short duration of action at normal doses.

Since neuromuscular monitoring was not available at the time of surgery, the anaesthetist was led to believe the induced neuromuscular block was inadequate following apparent limb movement. The patient received a top-up with mivacurium (4 mg), although on later investigation it was ascertained that the patient’s movements had resulted from manual adjustment of the limbs beneath the drapes.

This patient received enflurane anaesthesia which can decrease the ED₉₀ dose of mivacurium by as much as 25%, and which may have contributed to the long duration of drug action. Other than mivacurium and enflurane, the patient received fentanyl 25 mg IV, propofol 70 mg IV, chlorpheniramine 10 mg IV, ketorolac 30 mg IV and dimenhydrinate 50 mg IV, none of which have been reported to interact with mivacurium.

Without a contributory past or family history there was no reason prior to surgery to suspect a pharmacogenetic aberration in the metabolism of mivacurium. Mivacurium is hydrolyzed by plasma pseudocholinesterase, (to be differentiated from true or acetylcholinesterase which hydrolyzes acetylcholine) which is inhibited by dibucaine. The dibucaine number is a simple test which determines the percentage inhibition of pseudocholinesterase and indicates the presence of the normal or atypical enzyme. Based on the dibucaine number, Kalow and Staron divided the population into 3 classes. Individuals with a dibucaine number between 71-90 are homozygous for the typical E/E₀ gene and have normal enzyme activity, where E₀ is the gene which controls production of cholinesterase. Those with a dibucaine number below 20 are homozygous for the atypical E/E₀ gene, while individuals who are heterozygous for the normal and the atypical gene have an intermediate dibucaine number between 40-70. A dibucaine number of 53 in this patient suggests she has a heterozygous and thus would not produce physiologically normal pseudocholinesterase. Mivacurium-induced neuromuscular blockade is reported to be significantly prolonged in patients heterozygous for the atypical cholinesterase gene.

This patient's cholinesterase level was 0.93 U/mL, much below the reported enzyme activity of between 9.03-10.79 U/mL in Trinidadian females. In females of mixed heritage in Trinidad, esterase activity is 10.24 ± 2.91 U/mL, many times higher than the enzyme activity in this patient who confirmed her ethnicity comprised Asian Indian, African and Chinese descent.

In conclusion, we believe the etiology of this patient's prolonged mivacurium block resulted from genetic determinants, high dosing and a drug-interaction with enflurane. She was heterozygous for the atypical cholinesterase gene with low enzyme activity. The altered esterase activity in this patient suggests a family study be initiated to determine the presence and inheritance of the variant esterase activity. Her recovery may have also been delayed by enflurane which has central and postjunctional neuromuscular blocking effects. In addition, this patient received an excessive dose of mivacurium which may have been avoided if a neuromuscular monitor was available.

For those neuromuscular blocking agents that are metabolized by pseudocholinesterase, anesthetists should be aware that pharmacogenetic aberrations of metabolism from altered enzyme activity will delay the recovery of spontaneous ventilation. Fortunately, these situations cannot be predicted by test doses. Careful anesthetic history of the patient and the family should be elicited, as well as the exclusion of hepatic pathology which can alter pseudocholinesterase production. Though mivacurium-induced respiratory muscle paralysis can be reversed by neostigmine, a neuromuscular monitor is an essential requirement when using neuromuscular blocking drugs.

**REFERENCES**

2. Savarese JJ, Aii HH, Basta SJ, Embree PB, Scott RPF.


12. Product Monograph. Mivacron®. Wellcome Medical Division, Burroughs Wellcome Inc., Quebec, Canada, 1995; August.
