Prolonged Neuromuscular Block in Two Patients Undergoing Abdominal Surgery

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Citation

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Abstract

Neuromuscular blockade has the potential to be prolonged when using medications metabolized by serum pseudocholinesterase (i.e., succinylcholine or mivacurium). Patients who demonstrate an abnormal genetic variant, a decrease in concentration by seventy-five percent, or who are exposed to chemicals or medications that block or reduce the serum concentration of pseudocholinesterase will potentially experience prolonged duration of action. When faced with prolonged action of succinylcholine, it is important to provide supportive therapy until there is full return of neuromuscular function. Following resolution, patients should be tested and then counseled regarding the findings. We cared for two patients at our institution, within a one month period, who exhibited prolonged duration of action with succinylcholine. We review these cases, and describe the current issues associated in dealing with patients with pseudocholinestersase deficiency.

INTRODUCTION

Neuromuscular blockade has the potential to be prolonged when using medications metabolized by serum pseudocholinesterase (i.e., succinylcholine or mivacurium). Pseudocholinesterase, found in plasma and connective tissue, is a tetrahedral molecule with a MW of 320,000, is formed in the liver, and has a half-life of approximately 8-16 hours. Patients who demonstrate an abnormal genetic variant, a decrease in concentration by seventy-five percent, or who are exposed to chemicals or medications that block or reduce the serum concentration of pseudocholinesterase will potentially experience prolonged action of succinylcholine and/or mivacurium.

We recently cared for two unrelated patients who exhibited prolonged action of succinylcholine. We review these cases, and describe the issues associated with pseudocholinestersase deficiency.

CASE REPORT

CASE 1

The patient was a 48 year old female who presented for a bowel resection. Her past medical history was unremarkable. The patient stated that she had no problems with her previous general anesthetics, however the records from these surgeries were not available for review. She had no known drug allergies. There was no family history of anesthetic complications. The patient's social history was significant for smoking. Physical exam revealed a well-hydrated, well-nourished female, 5'2" and 120 lbs. The patient was premedicated with 2 mg midazolam. She was then taken to the operating room, where standard ASA monitors were placed. After preoxygenation, a rapid sequence induction with 150mg propofol and 80 mg succinylcholine was performed. The patient underwent an exploratory laparotomy, segmental resection of ileum, and lysis of an omental band. Anesthesia was maintained with sevoflurane in oxygen. No further muscle relaxants were administered. The patient demonstrated no return of twitches fifteen minutes after succinylcholine administration, and a pseudocholinesterase deficiency was suspected. There continued to be no clinical evidence of recovery of neuromuscular function, although train of four stimulation was monitored frequently, until completion of the procedure 30 minutes later. At this point, the patient had regained one twitch in response to train-of-four stimulation. The patient was transferred to the post anesthesia care unit (PACU) with her trachea intubated for continued mechanical ventilation and neuromuscular monitoring. The patient was sedated with a propofol infusion (25 mcg/kg/min) in the PACU. Two hundred and ten minutes after the initial administration of succinylcholine, clinical assessment confirmed recovery of neuromuscular function. The propofol infusion was discontinued, the patient's trachea was extubated and the

remainder of the hospital stay was uneventful. Postoperatively, the plasma cholinesterase level was 297 (normal 1900-3800) and the dibucaine number was 35.

The patient was notified of her condition and was counseled regarding the clinical significance, how her future anesthetics would be affected, and the possibility of need for a medic alert bracelet. We also suggested that the patient's first degree relatives be tested for this condition. This conversation was documented in the patient's chart as well as in a letter which was sent to the patient.

CASE 2

The patient was a 24 year old multiparous female who reported to our same day surgical center for laparoscopic tubal ligation. She was a 5'6" 141 pound female with history of multiple vaginal deliveries without complications. She was on no medications and had no significant medical history. In addition, neither she nor any of her family members had a history of prior surgical or anesthetic complications. The physical exam demonstrated a slightly obese Hispanic female with a Malampati Class I airway. Urine pregnancy test was negative. The patient was premedicated with 2mg intravenous midazolam. The patient was induced with 200mg of propofol and 100mcg of fentanyl; 100mg of succinylcholine was administered to facilitate intubation of the trachea. Anesthesia was maintained with sevoflurane and nitrous oxide in oxygen. The train-of-four was checked at 5 minute intervals following administration of the succinylcholine. The patient displayed no return of twitches during the case. No additional muscle relaxants were administered. One hour following succinylcholine administration, a slight return of twitches was present. There was fade in response to train-of-four stimulation, consistent with phase II blockade. The patient was unable to regain sufficient muscle strength at conclusion of the case and was transported with her trachea intubated to the post anesthesia care unit (PACU) for continued mechanical ventilation and neuromuscular monitoring. She received 2mg midazolam and a propofol infusion (10-20 mcg/kg/min) for sedation. Forty minutes later, the response to train-of-four stimulation appeared normal. The propofol infusion was stopped, and she regained sufficient muscle strength to generate appropriate negative inspiratory force and adequate tidal volume. The patient's trachea was then extubated without complication. The patient had no recall of the preceding events and was discharged uneventfully. The laboratory tests drawn prior to her discharge were as follows: pseudocholinesterase level was 794; and the dibucaine number was 37. The patient was notified of her condition and was counseled regarding the incident and of its clinical significance.

DISCUSSION

In the early 1950s, it was demonstrated that some individuals had prolonged action of succinylcholine, and that this variance was hereditarily transmitted. ($_1$) Susceptibility to prolongation of action could be predicted in these families via pedigree analysis. It was not until 1957 when qualitative and quantitative differences in the pseudocholinesterase enzyme were shown to determine the duration of succinylcholine apnea ($_2$). They found that patients with prolonged succinylcholine activity showed increased resistance to the inhibitory effects of dibucaine on the hydrolysis of a benzylcholine substrate. This data led to the development of the utilization of a "dibucaine number" to represent the percentage of the enzyme reaction inhibited. ($_2$) Less enzyme inhibition corresponds to greater atypical enzyme. (Table 1) Although the dibucaine number indicates the genetic make-up of an individual with respect to pseudocholinesterase, it does not measure the concentration of the enzyme in plasma, nor does it indicate the efficiency of the enzyme itself. However, it does provide the percentage of enzyme inhibited which correlates to the duration of prolonged clinical action of the muscle relaxant.

Figure 1

Table 1

Dibucaine Number and Duration of Neuromuscular Blockade

Type of butyryl-cholinesterase	Genotype	Approx Incidence in European studies	Dibucaine Number (% inhibited)	Response to Succinyl-choline	Fluoride Number	Cholinesterase Activity
Homozygous typical	E_uE_u	96%	78-86	Normal	55-65	Normal
Homozygous atypical	E_aE_a	.05%	18-26	Prolonged 4-8 hours	16-32	Low
Heterozygous atypical	E_uE_a	2.5%	51-70	Lengthened by 50-100%	38-55	Moderate
Heterozygous fluoride variant	E_uE_f	0.3%	74-80	Similar to E_uE_a	47-48	Moderate
Heterozygous atypical fluoride variant	E_fE_a	.005%	49-59	Similar to E_aEa	25-33	Low
Heterozygous fluoride and silent variant	E_fE_s	.006%	63	Similar to E_aEa	26	Low

There are four variants described: E^u 1 (usual); E^f 1 (fluoride resistant); E^a 1 (atypical); and E^s 1 (silent)(Table 1,3). The fluoride variant refers to pseudocholinesterase's inhibition in the presence of fluoride. A fluoride number (analogous to dibucaine number) will demonstrate the

percent inhibition of the enzyme to fluoride. When the silent variant is present, the pseudocholinesterase enzyme is not produced ([3]). In 1991 a single gene locus was identified on chromosome 3, allowing molecular genetics techniques to be used for investigations in patients with decreased acetylcholinesterase activity.([4, 5]) Three other quantitative gene variants (E^K 1, E^J 1, E^H 1) have since been described ([6]). These variants commonly exist, however, they produce a decreased level of enzyme with normal activity and no clinical prolongation of action ([6]). When unusual genotype combinations exist, other known inhibitors such as bromide, urea, and sodium chloride, may be helpful in clarifying the specific abnormality. These may cause decreased enzyme concentration with normal activity, however they commonly produce little or no clinical effect. The occurrences of these genetic differences vary to some extent with ethnic backgrounds. For example, Alaskan Eskimos have a gene frequency for pseudocholinesterase deficiency in excess of 10% (of the silent gene variant) ([7]). Also of note, South African blacks have a higher incidence of the silent variant ([8]), patients with Huntington's chorea have a higher incidence of fluoride resistance, and people of Israeli decent have a higher incidence of the atypical variant. ([3]) In addition to these primary genetic enzyme deficiencies, secondary enzyme deficiencies are well known. Decreased enzyme activity may be due to physiologic, pharmacologic or pathologic conditions. Some examples include: gender (lowest in women ages 16-50) ([9]), pregnancy ([10]), reduced activity of the newborn ([11]), pharmacology- via irreversible (echothiophate- within two weeks of discontinuation) or reversible inhibition of pseudocholinesterase [e.g. pyridostigmine, cyclophosphamide (dose dependent), and pesticides] ([12]), age ([13]), and various pathological states including severe liver disease and malnutrition ([14]). Although each of these may prolong succinylcholine's action, the significance of each should be evaluated in each individual patient. For example, age and pregnancy may not be the primary cause in a patient with decreased production from liver disease. Acquired deficiency becomes clinically evident when there is a >75% decrease in normal pseudocholinesterase level ([15]).

Given that the incidence of homozygous deficiency in the general population is 1:3,200, caring for two unrelated patients with pseudocholinesterase deficiency in a one month period at one institution is highly unlikely. Also, despite our questioning, neither of our patients presented with a personal or family history of anesthesia related complications suggesting few surgeries in recent generations or no communication of prolonged neuromuscular blockade among family members. Our patients had both a decreased serum cholinesterase level and dibucaine number. The low dibucaine numbers confirm that both patients have the atypical variant. The technology for the diagnosis of pseudocholinesterase deficiency has made significant advances as mentioned above. Specific testing exists for the identification of atypical variants includes obtaining DNA samples from patient leukocytes. The specific atypical mutation on chromosome 3 has been elucidated ([4, 5]). The amino acid substitution [aspartic acid Glycine (GAT GGT) associated with MboI site deletion at position 434], can be tested via polymerase chain reaction amplification ([16]); however, this is not a commercially available option. Only a few research based facilities are able to conduct this testing, and outside sampling diagnostics are not usually conducted. The Danish Cholinesterase Research Unit in Copenhagen, Denmark accepts outside patient samples for evaluation (Dr. Jørgen Viby-Mogensen; personal communication). However, coordinating these results into clinical practice may be difficult because international labs may not be accredited by CLIA (Clinical Laboratory Improvements Act) and therefore the results may not be accepted by US clinical laboratories. Furthermore, the clinical treatment of these patients is not affected by knowledge of the specific genetic variation.

Our patients were counseled regarding future anesthesia, particularly the receipt of succinylcholine and mivacurium ([17]). Since significant prolongation can be expected in patients with these genetic variations, consideration should be given to suggesting these patients wear medic alert bracelets (http://www.MedicAlert.org); however, there is no clear consensus regarding the recommendation of wearing a medic alert bracelet. Dr. Viby-Mogensen and his research unit advise these patients to carry a warning card which contains the DNA findings (Dr. Jørgen Viby-Mogensen; personal communication). If a deficiency is considered a possibility in any patient, it would seem prudent to avoid succinylcholine or mivacurium. In such a case, when rapid sequence induction is planned, one should be prepared for the unanticipated difficult to intubate / ventilate patient when given a longer acting non-depolarizing muscle relaxant (e.g., rocuronium). Having advanced airway equipment, including a fiberoptic bronchoscope, a rigid intubating bronchoscope (e.g., Bullard laryngoscope) and an intubating laryngeal mask airway, may prove lifesaving([18]).

When faced with prolonged action of succinylcholine, it is important to provide supportive therapy until there is full return of neuromuscular function. It is necessary to provide sedation to these patients while awaiting return of function; a propofol infusion is ideal for this purpose. Following resolution, patients should be tested and then counseled regarding the findings. It is controversial whether blood relatives should undergo testing, although this should be offered. The conservative approach would be to assume that first degree blood relatives have a similar abnormality of pseudocholinesterase function.

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