Prolonged Neuromuscular Block in a 74-Year-Old Patient

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Pseudocholinesterase abnormalities are an inherited trait, which causes aberrant metabolism of certain ester-based drugs. This anomaly poses the greatest risk for patients undergoing anesthesia when providers use the muscle relaxant succinylcholine because of its characteristic short duration of action. This abnormal metabolism can necessitate prolonged intubation, for greater than 8 hours in some cases. Depending on the type of surgical facility, this aberration can pose difficulties with case management. With the growing trend for freestanding surgical centers, the stage is set for additional complications because these facilities are unable to accommodate prolonged intubation with mechanical ventilation. This case study examines a single case of pseudocholinesterase insufficiency, which necessitated hospital admission to the intensive care unit until adequate recovery was achieved. It is important to educate affected individuals, as they may require general anesthetics for future procedures in which succinylcholine might be administered for laryngoscopy.

Keywords: Dibucaine number, prolonged apnea, pseudocholinesterase deficiency.

Use of the depolarizing neuromuscular blocker succinylcholine is common practice to facilitate tracheal intubation. Succinylcholine and certain other drugs are metabolized by serum pseudocholinesterase (PChE). Upon administration, succinylcholine is hydrolyzed rapidly into succinylmonocholine by PChE. Succinylmonocholine, a weaker neuromuscular blocker than succinylcholine, is metabolized into succinic acid and choline. Because of the rapid metabolism of succinylcholine in the plasma by PChE, only a small fraction of the dose injected actually reaches the neuromuscular junction.\(^1\)\(^2\) The succinylcholine that does reach the neuromuscular junction diffuses away rapidly as serum concentrations fall, thus limiting the duration of action. When PChE in the plasma is deficient or present in insufficient amounts, more of the administered succinylcholine reaches the neuromuscular junction (NMJ) and neuromuscular blockade can be prolonged.\(^3\) We present a case of a patient with no previously diagnosed PChE deficiency who required extended mechanical ventilation after receiving succinylcholine.

Case Summary

A 74-year-old woman presented for elective laparoscopy with salpingo-ophorectomy, to be performed under general anesthesia. The patient was 163 cm tall and weighed 80 kg. She reported a history of hypertension, gastroesophageal reflux disease, and anemia. Current medications included lisinopril, omeprazole, temazepam, and ceterizine. She had no known drug allergies but reported that sulfa-containing drugs caused nausea. Routine complete blood cell count and results of a basic chemistry profile were within normal limits. She reported a past surgical history of tonsillectomy, colonoscopy, carpal tunnel release, cataract excision, breast lumpectomy, and most recently a lumbar fusion procedure. She denied any adverse outcomes with previous anesthetics or any family history of anesthetic complications. Physical examination revealed a white woman in no acute distress. The patient was premedicated with 1 mg of midazolam.

She was then taken to the operating room, where standard physiologic monitors were placed. After preoxygenation, intravenous (IV) induction was carried out with 100 mg of propofol and 100 μg of fentanyl; 140 mg of succinylcholine was administered to facilitate intubation of the trachea with 5 mg of rocuronium given beforehand to reduce fasciculations. Anesthesia was maintained with sevoflurane in oxygen with mechanical ventilation. No additional muscle relaxants were administered. Neuromuscular blockade was monitored approximately 10 minutes after induction by transcutaneous stimulation of the orbicularis oculi muscle via the facial nerve. There was no twitch response to train-of-four (TOF) or tetany stimulation. The TOF stimulation was monitored frequently, with no clinical evidence of recovery of neuromuscular function by the end of the surgical procedure 45 minutes later.

The patient was transferred to the postanesthesia care unit (PACU) without extubation for continued mechanical ventilation and monitoring of her neuromuscular status. The anesthetic agent was maintained until all preparations were completed for transfer of the patient.
to the PACU. Immediately prior to transport, she was sedated with an additional 2 mg of midazolam and 100 μg of fentanyl. Upon arrival at the PACU, sedation was continued with an infusion of propofol beginning at 10 to 20 μg/kg/min and titrating up as indicated for comfort and continued sedation.

Approximately 2 hours after administration of succinylcholine, with the patient still exhibiting no substantial muscle response, she was admitted to the intensive care unit (ICU). More than 360 minutes after administration of succinylcholine, the patient began to show purposeful movement. Her motor activity and muscle strength continued to improve overnight, and she was weaned from both the propofol and mechanical ventilation. Upon meeting satisfactory extubation criteria the following morning (postoperative day 1), she was extubated. Continued observation over the next few hours showed no further respiratory compromise, and she was subsequently discharged without further complication.

Laboratory tests drawn prior to the patient’s discharge revealed the following: pseudocholinesterase activity level was 413 U/L, and the dibucaine number was 35. These test results indicate that the patient would be expected to always exhibit a prolonged response to succinylcholine. The patient was counseled regarding the clinical significance of the condition, as it may relate to future anesthetic concerns, and was advised to consider the need for a medic alert bracelet. In addition to this conversation, a letter was sent to the patient. Following a signed release, examination of the patient’s previous medical records revealed that she had not received a depolarizing neuromuscular relaxant for her most recent surgeries.

**Discussion**

This report summarizes the perioperative events of a patient with previously undiagnosed pseudocholinesterase deficiency and whose anesthetic included the administration of succinylcholine. A PChE enzyme deficiency was suspected after failure to elicit a muscle twitch response following a single dose of succinylcholine. Although the patient had reported no prior problems with anesthesia, subsequent laboratory testing confirmed a PChE deficiency.

Pseudocholinesterase, plasma cholinesterase, or nonspecific cholinesterase, is an enzyme that is synthesized in the liver and found in plasma and most tissue but not in red blood cells. Pseudocholinesterase is distinct from acetylcholinesterase (AChE), which is found in nerve endings and in red blood cells (Figure). Acetylcholinesterase is concentrated in the NMJ and hydrolyzes acetylcholine (ACh). The catalytic activity of AChE is very high; each molecule of AChE degrades about 25,000 molecules of ACh per second. The number of molecules degraded is referred to as the activity of the enzyme. The choline produced by the action of AChE is recycled; it is transported, through reuptake, back into nerve terminals, where it is used to synthesize new ACh molecules. The physiologic function of PChE in mammals, including humans, is currently unknown. Pseudocholinesterase does, however, metabolize suc-
cinylcholine, a depolarizing neuromuscular blocking agent. A deficiency in the enzyme (atypical PChE) or an inadequate amount of PChE may not be identified until the individual is either tested specifically for a PChE abnormality or experiences prolonged effect from exposure to a substance normally metabolized by PChE.

It is important to note that an individual may have either an inadequate amount (decreased level) of PChE or a deficiency of the enzyme (normal level but decreased activity), or both. There are many factors that can either increase or decrease the activity of this enzyme, including physiologic, pharmacologic, and pathologic factors (Table 1). Because PChE is synthesized in the liver, decreased levels of the enzyme may result from advanced cases of hepatocellular dysfunction. Viby-Mogensen determined that apnea is only moderately prolonged with as much as a 70% depression in PChE activity and that apnea is significantly prolonged only with extreme PChE depression.

Atypical PChE is of concern to the anesthesia provider because of the possible resultant duration of action of succinylcholine and, in some cases, ester-linked local anesthetics. In patients who have very low absolute activity of PChE or who have variants of the enzyme, prolonged apnea after succinylcholine administration may occur.

A search of the literature shows that Kalow and Genest demonstrated in the 1950s that some individuals had a hereditarily transmitted prolonged action of succinylcholine and that there were quantitative as well as qualitative differences in the PChE enzyme. It is these differences that determine the duration of apnea after administration of succinylcholine. The amount of PChE activity is determined by colorimetric assay using benzylcholine substrate. These assays determined that in persons showing succinylcholine sensitivity, the hydrolysis of the benzylcholine substrate was inhibited less by the local anesthetic dibucaine than in persons with a normal response to succinylcholine. Thus, they are termed dibucaine-resistant. The dibucaine number is used to refer to the percentage of inhibition. The abnormal enzyme has only about 1/200 the affinity for dibucaine than the normal PChE. The dibucaine number was found to be constant for a person and was not dependent on the enzyme concentration. The dibucaine numbers have a discontinuous distribution, suggesting an inheritance pattern based on alteration at a single gene locus. Individuals with a dibucaine number of 80 are considered homozygous normal and would have a normal response to succinylcholine. Those with dibucaine numbers of 20 would be homozygous atypical and would exhibit a marked prolongation of succinylcholine activity (greater than 1 hour), whereas persons with dibucaine numbers in the 60 range would be heterozygous and usually exhibit only a slight prolongation of the effects of succinylcholine.

Although the dibucaine number is a good indicator of the genetic makeup of persons with regard to their PChE status, it does not measure the enzyme concentration in plasma or the efficiency of the enzyme itself. The dibucaine number is proportional to the function of PChE but is independent of the amount of the enzyme. Therefore, the adequacy of the PChE is determined in the laboratory qualitatively by the dibucaine number and quantitatively (PChE level) in units per liter. The activity of plasma cholinesterase can be measured by adding plasma to benzylcholine and following the reaction spectrophotometrically. Abnormally low values can be further investigated for phenotype by carrying out the reaction in the presence of certain other inhibitors, such as sodium fluoride and a specific inhibitor known as Ro2-0683. However, it is important to note that with certain substances there is no correlation between the measured PChE activity (in patients with genetically abnormal enzymes) and the recorded duration of action of succinylcholine. Viby-Mogensen, who has published extensively on pseudocholinesterase deficiency, cautions that even in laboratories with extensive experience in biochemical testing for abnormal phenotypes, there is sometimes considerable variation in the dibucaine number (Jørgen Viby-Mogensen, MD, written communication, November 15, 2009). The only definitive way to establish a correct genotype is with modern molecular genetic methods.

<table>
<thead>
<tr>
<th>Acquired factors causing an increase</th>
<th>Acquired factors causing a decrease</th>
<th>Drugs and chemicals causing a decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Pregnancy</td>
<td>Neostigmine</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Liver disease</td>
<td>Pyridostigmine</td>
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<tr>
<td>Thyrotoxicosis</td>
<td>Malnutrition</td>
<td>Chlorpromazine</td>
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<tr>
<td>Psoriasis</td>
<td>Myxedema</td>
<td>Echothiopate</td>
</tr>
<tr>
<td>Electroshock therapy</td>
<td>Cancer</td>
<td>Cyclophosphamide</td>
</tr>
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<td></td>
<td>Acute infection</td>
<td>Pancuronium</td>
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<tr>
<td></td>
<td>Myocardial infarction</td>
<td>Organophosphorus insecticides</td>
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</tbody>
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Table 1. Factors That Change Pseudocholinesterase
In 1964, Lehmann and Liddell concluded that there are 4 allelic genes responsible for the inheritance of PChE activity. The 4 genes are: N, the “normal” gene (for normal PChE activity); D, the atypical variant gene (altered response to the inhibitor dibucaine); F, the gene for an enzyme with an altered sensitivity to fluoride inhibition; and S, the “silent” gene responsible for complete absence of any PChE activity. The gene that codes for the pseudocholinesterase enzyme is located at the E1 locus on the long arm of chromosome 3, and 96% of the population is homozygous for the normal pseudocholinesterase genotype, which is designated as EuEu. The remaining 4% of the population carries 1 or more of the following atypical gene alleles for the pseudocholinesterase gene in either a heterozygous or homozygous fashion: Ea (for atypical) or Ed (for dibucaine); Ef and Es alleles may occur in the homozygous form or in any heterozygous combination with each other, with the normal Eu allele, or with a number of additional rare variant abnormal alleles (Table 2). These gene combinations reveal the presence or absence of the atypical enzyme but do not give any information on the enzyme concentration or activity level. Viby-Mogensen labels these gene combinations, together with their usual activity levels and dibucaine numbers, as shown in Table 3. The genotypes that have the highest correlation of activity levels and dibucaine numbers, as shown in Table 3. The genotypes that have the highest correlation of activity levels and dibucaine numbers, as shown in Table 3.

### Table 2. Atypical Gene Alleles for Pseudocholinesterase Genotype

<table>
<thead>
<tr>
<th>Gene allele</th>
<th>Variant</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ea or Ed</td>
<td>Atypical, dibucaine-resistant variant</td>
<td>Point mutation</td>
</tr>
<tr>
<td>Ef</td>
<td>Fluoride-resistant variant</td>
<td>Point mutation</td>
</tr>
<tr>
<td>Es</td>
<td>Silent variant</td>
<td>Frameshift mutation</td>
</tr>
</tbody>
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Abbreviations: Ea, atypical enzyme gene; Ed, dibucaine resistant gene; Ef, fluoride-resistant gene; Es, silent gene.

### Table 3. Pseudocholinesterase Gene Combinations With Their Inherent Activity Levels and Dibucaine Number

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Activity (U/L)</th>
<th>Dibucaine no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EuEu</td>
<td>677 - 1,860</td>
<td>78 - 86</td>
</tr>
<tr>
<td>EAEa</td>
<td>140 - 525</td>
<td>18 - 26</td>
</tr>
<tr>
<td>EuEa</td>
<td>285 - 1,008</td>
<td>51 - 70</td>
</tr>
<tr>
<td>EuEf</td>
<td>579 - 900</td>
<td>74 - 80</td>
</tr>
<tr>
<td>EfEa</td>
<td>475 - 661</td>
<td>49 - 52</td>
</tr>
<tr>
<td>EfEs</td>
<td>351</td>
<td>63</td>
</tr>
</tbody>
</table>

Abbreviations: Eu, normal (usual) enzyme gene; Ea, atypical enzyme gene; Ef, fluoride-resistant enzyme gene; Es, silent gene.

to 8.6 minutes, an increase that is usually of no clinical significance.

There are various pharmacologic and chemical agents that may cause acquired PChE deficits. Acetylcholinesterase inhibitors, such as pancuronium and echothiophate eye drops inhibit PChE. Pancuronium is a nondepolarizing neuromuscular blocking agent (NMB). Nondepolarizing neuromuscular blockers function by binding to the ACh receptor at the NMJ as a competitive inhibitor of the channel but are unable to cause opening of the channel. This is important because anesthesia providers may use a subparalytic dose (10% to 15% of the intubating dose) of a NMB prior to administering succinylcholine, in an effort to reduce fasciculations and thus reduce postoperative myalgia. Ivankovich et al showed an association of a decreased level of pseudocholinesterase with a pretreatment dose of 1.5 mg of pancuronium, resulting in potentiation of neuromuscular blockade with Sch. Interestingly, although pancuronium blocks PChE, it is not affected by it. Other drugs, such as steroids, can cause decreased PChE synthesis. Certain chemotherapeutic agents, most notably cyclophosphamide, is also known to inhibit PChE. Koseoglu et al reported a case of a young girl who maintained flaccid paralysis and required ventilator support for 90 minutes after receiving succinylcholine within 9 hours after a high-dose regimen of chemotherapy that included cyclophosphamide. Organophosphate insecticides also inhibit AChE. Anyone exposed to cholinesterase-affecting pesticides can develop lowered cholinesterase levels; therefore, it is recommended that these persons have their cholinesterase levels checked on a regular basis.

In addition to genetic testing, several laboratory tests can be performed to determine the activity of the pseudocholinesterase enzyme. Humans have 3 types of cholinesterase: AChE (red blood cell cholinesterase, true cholinesterase), plasma cholinesterase (pseudocholinesterase) and brain cholinesterase. Although AChE is located in the nervous system, plasma cholinesterase is synthesized...
in the liver and circulates in the plasma. Laboratory methods for cholinesterase testing differ greatly, and results obtained by one method cannot be easily compared with results obtained by another. Sometimes there is also considerable variation in test results between laboratories using the same testing method. Cholinesterase levels vary greatly within an individual, between individuals, between test laboratories, and between test methods. Whenever possible, cholinesterase monitoring for an individual should be performed in the same laboratory, using a consistent testing method. The approved methods are the delta pH method by Michel (1949), the kinetic assays pioneered by Ellman and colleagues (1961), and certain variations.19

In the event of prolonged succinylcholine action, treatment is to provide supportive therapy until full neuromuscular function returns. While awaiting return of function, sedation may be necessary. Recovery occurs as a result of passive diffusion of succinylcholine away from the neuromuscular junction. Although 2 U of blood may contain adequate amounts of PChE to hydrolyze the succinylcholine, blood transfusion is not a totally benign process and is not recommended for routine treatment of apnea induced by succinylcholine.6 Similarly, administration of cholinesterase inhibitors, such as neostigmine, for reversing succinylcholine-induced apnea is controversial and thus not recommended, as the effects may be transient and may be followed by intensified neuromuscular blockade.20 After identification, patient education is paramount so that medications metabolized by PChE can be avoided in future anesthetic experiences.

Conclusion

Deficiency of PChE, either inherited or acquired, can have unexpected results regarding the patient’s ability to metabolize certain drugs. This case report described a 74-year-old woman who experienced apnea from prolonged neuromuscular blockade because of a decreased PChE activity level of 413 U/L and a dibucaine number of 35, indicating an abnormal PChE level as well as a PChE deficiency. Individuals who unknowingly possess this anomaly pose a great challenge to anesthesia providers because of the diverse and unexpected duration of action of succinylcholine. This anomaly poses a grave concern, particularly in freestanding surgical centers when the patient may need hospital admission.

REFERENCES


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