Abstract

Pseudocholinesterase deficiency manifests as prolonged motor blockade after the administration of succinylcholine. A previously unknown homozygous form of the disease, became apparent during a lumbar laminectomy seriously limiting the ability to monitor motor evoked potentials and perform electromyelography (EMG). Moreover, concerns were raised as to how the enzyme deficiency would affect the metabolism of remifentanil and other esters during a total intravenous anesthetic. We present the perioperative management of the patient and a literature review of the syndrome.

The patient provided written permission for the authors to publish this report. At our institution, IRB review and approval is not required for a single case report.

Introduction

A major anesthetic concern in caring for patients undergoing spine surgery with pedicle screw placement is the ability to obtain optimal motor, sensory, and EMG evoked potentials. Our patient was diagnosed intraoperatively with a pseudocholinesterase deficiency, which, due to the administration of succinylcholine, prevented both the monitoring of motor, and EMG evoked potentials, and which precluded an immediate postoperative neurologic assessment of the patient.

Case Presentation

An 89 year old female presented with chronic back pain and spinal stenosis for an L2 – S1 laminectomy and fusion. She gave a history of elevated serum cholesterol, type II diabetes, and hypertension. In recent years, she had undergone surgeries on her right thumb and breast which were both uneventful and likely performed without muscle relaxation with succinylcholine. A half-century prior she had two other surgeries: a total abdominal hysterectomy and an appendectomy.
after both of which she described being “sleepy and hard to wake up.” Owing to the ensuing 50 year time interval, the patient was unable to provide any further detail or records about those procedures. She had stated allergies to aspirin and penicillin.

The patient was brought to the operating room, and after sedation with fentanyl and midazolam, anesthesia was induced with propofol and succinylcholine. Her trachea was easily intubated, and infusions of propofol and remifentanil were immediately started for the maintenance of anesthesia. She was soon placed in the prone position, at which time multiple electrodes were placed to enable neurophysiologic monitoring of somatosensory, motor and EMG evoked potentials.

After the surgeons prepped and draped the surgical field, the neurophysiologist obtained baseline measurements. At this point, approximately forty minutes after induction, we were made aware that the patient had no peripheral motor twitches. We independently verified this finding with a peripheral nerve stimulator, and notified the surgeon that we had a presumptive diagnosis of pseudocholinesterase deficiency, which would preclude intraoperative motor and EMG evoked potential monitoring. As the patient was already anesthetized and we were able to obtain good baseline sensory evoked potentials, the surgeon made the decision to proceed with the planned operation.

Approximately one hour and forty five minutes after succinylcholine administration, we were able to obtain one twitch on a train of four, which is consistent with a diagnosis of homozygous pseudocholinesterase deficiency, which would preclude intraoperative motor and EMG evoked potential monitoring. As the patient was already anesthetized and we were able to obtain good baseline sensory evoked potentials, the surgeon made the decision to proceed with the planned operation.

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Discussion

Pseudocholinesterase, also known as butyrylcholinesterase, is one of many esterases in man. While its native purpose is unclear, it does interact with several exogenous esters. The two most commonly explored and publicized are succinylcholine and mivacurium, both of which are rapidly broken down by pseudocholinesterase. As such, they have been used for several years in the field of anesthesiology to provide neuromuscular blockade with a rapid onset and short lived effect. In our patient, succinylcholine was used at induction with the expectation that it would wear off swiftly so that monitoring of motor and EMG evoked potentials could proceed unhindered.

The gene which codes for pseudocholinesterase is the BCHE gene, located on chromosome site 3q26. Any mutation to this gene can lead to decreased enzyme function and a clinical pseudocholinesterase deficiency. Several documented mutations have been found to lead to varying levels of pseudocholinesterase activity. At least 5 alleles are known to cause an easily identifiable decrease in enzyme activity, with 65 named variants causing mild to extreme pseudocholinesterase paralysis. New alleles are discovered frequently, including two in 2008. While heterozygous mutations of this allele lead to mildly decreased pseudocholinesterase effect, patients who carry homozygous mutations show severely decreased pseudocholinesterase function.

In the general population approximately 4% of people carry at least one mutated allele of the BCHE gene, and approximately 1:3000 are homozygous for abnormal alleles. However, the incidence of pseudocholinesterase deficiency can vary widely in different populations. For example, the Vysya community in India has been found to have a homozygous mutation incidence of 2-4%. Our patient was clearly homozygous for abnormal alleles clinically extubated. Examination at this time revealed intact motor and sensory function in all four extremities. She was discharged to a rehabilitation facility as planned several days postoperatively.
although we were unable to confirm the diagnosis by
genotyping we followed her motor function, with one
twitch returning two hours after dosing and full power
returning after approximately eight hours.

In a patient with a known pseudocholinesterase
deficiency, the administration of agents dependent
on pseudocholinesterase for metabolism can be
avoided, thus sidestepping any potential problems.
Unfortunately, despite reaching the age of 89 and
having had several prior surgeries, our patient had
not previously been diagnosed. While the surgeon
expressed amazement at this apparent lapse, our
lack of understanding of the native function of
pseudocholinesterase implies that, in the absence of
the administration of an ester drug, a person carrying
a mutation in this gene may never receive a diagnosis.
Had we known about her condition, our initial muscle
relaxation could have been achieved with other non
depolarizing agents, in doses titrated to wear off prior
to the initiation of monitoring.

Of note, is her prior anesthetic history. While it is
impossible to know exactly which agents she received
in the early 1960s, the description of post operative
“sleepiness” is different from one of actual muscle
relaxation, although lacking further narrative, delayed
awakening might be consistent with some degree of
continued paralysis. It is possible at that time that
she was anesthetized with ether and succinylcholine
was almost universally used for intubation. The
recommended treatment for prolonged paralysis
secondary to pseudocholinesterase deficiency is
supportive. Patients remain apneic secondary to
paralysis of the diaphragm, and therefore mechanical
ventilation must be maintained until spontaneous
respiration resumes. Given the rarity of the condition,
there are few treatment options. However, a literature
search provides a few possible choices, some
theoretical, and others clinically proven.

Difficulty arises in diagnosing pseudocholinesterase
deficiency, as our current
screening tests are both imperfect, and seldom
administered. Several mutations can cause clinical
pseudocholinesterase deficiency. The mainstay of
detection is the dibucaine number, but this is only
effective in certain genotypes. With genetic testing
becoming more affordable and widespread, it is
likely that it will completely replace the dibucaine
number as the preferred means of detection of any
pseudocholinesterase deficiency; at this point it is too
expensive to consider genetic testing on everyone who
may possibly require succinylcholine use.

Pseudocholinesterase exists in circulating plasma.
This sparked the idea that perhaps it may still be present
and active in stored blood or fresh frozen plasma.
Epstein et al tested the activity of pseudocholinesterase
in bank blood. By measuring pre-donation
pseudocholinesterase activity, then measuring its
activity in that same blood after storage for 21 days
in acid-citrate-dextrose-anticoagulant solution, the
authors found that it only lost about 15% of its activity.
While this was statistically significant, it was found
not to be clinically significant, as it led to an increase in
apneic time after succinylcholine administration from
three minutes to 3.6 minutes. No reason was found
for the decreased activity, but Calloway et al theorized
that it was due to the fact that red blood cells were
present in the whole blood. The data from Epstein
et al shows that indeed, when red blood cells and
plasma were immediately separated after donation,
pseudocholinesterase activity remained stable. The
results of these studies indicate that transfusion of
whole blood or FFP are likely viable options in treating
prolonged paralysis secondary to pseudocholinesterase
deficiency as such transfusions would provide the
patient with sufficient pseudocholinesterase activity to
metabolize the succinylcholine and end the prolonged
paralysis.

Another logical course of action is isolating
and administering pseudocholinesterase itself.
Several human enzymes are commercially available
and have been successful in treating a number of
enzyme deficiencies. Behringwerke, a Greman
pharmaceutical company, created a purified,
injectable form of human psuedocholinesterase. In
two separate studies, injection of 90-135mg of this
preparation led to a return of spontaneous ventilation
in 10 minutes. This dose was found to have
equivalent pseudocholinesterase activity to 500ml of
fresh human plasma in vitro. Other pharmaceutical
companies are attempting to find more cost efficient
ways to make recombinant pseudocholinesterase for general medical use. In 2007, one such company, Pharmathene, began using genetically modified goats to create pseudocholinesterase in large quantities. By genetically modifying the animals, they were able to make them excrete large quantities of pseudocholinesterase in their milk: approximately 2-3 grams per liter of milk.

As mentioned earlier, pseudocholinesterase is also responsible for the breakdown of ester local anesthetics including procaine, chloroprocaine, and, to a lesser extent, cocaine. As such, pseudocholinesterase deficiency is a relative contraindication to the use of these drugs. At least two case reports describe situations where epidural administration of chloroprocaine was prolonged, and its effects enhanced, in patients with low/abnormal pseudocholinesterase activity. It is clear that pseudocholinesterase is responsible also for the metabolism of cocaine; however, it has a much lower catalytic activity towards cocaine than it does towards succinylcholine. As such, there are several studies on modifying pseudocholinesterase to have a more profound breakdown of cocaine; thus making it useful in treating cocaine overdoses or preventing cocaine’s effects proactively. One such study by Xue et al found that a modified pseudocholinesterase mutant with a high catalytic activity towards cocaine could, in fact, be used as described above. Extending this to its theoretical conclusion, it is likely that different forms of synthetic pseudocholinesterase mutants could be created to rapidly metabolize any kind of ester.

In cases where neurophysiologic monitoring with motor, sensory, and EMG evoked potentials is necessary, it is important that the anesthetic agents do not interfere with said monitoring. As such, it is preferable that any neuromuscular blocker used is short acting, and will have worn off prior to incision so that accurate baseline neurophysiologic signals can be obtained. Such monitoring certainly requires the absence of any paralytic effect by the time the surgeon has finished his dissection and is ready for instrumentation. Similarly, it is important the use of volatile anesthetics are minimized as they may interfere with the monitoring. As such, the most commonly used method for these cases is a total intravenous anesthetic consisting of hypnotic and analgesic infusions. One common regimen, used in our case, is an infusion of propofol and remifentanil. Propofol has a predictable effect on neurophysiologic monitoring; as such it does not significantly affect the results and interpretation of those results. Remifentanil has no effect on monitoring and provides excellent intraoperative analgesia. Most importantly, remifentanil has a very short context sensitive half time in contrast to most other opioids. These properties are due to the fact that remifentanil is an ester and as such is broken down rapidly by several plasma esterases. Nelson et al described a case of prolonged emergence from anesthesia with remifentanil. It is known that extremes of age, liver function, and kidney function have minimal effects on its metabolism, however, it is possible that this delayed emergence was secondary to an esterase deficiency. As mentioned earlier, it is nonspecific esterases that are responsible for breaking down remifentanil; as such there are no tests for measuring their function. Similarly, there are no reports of a deficiency of one or more of these esterases in conjunction with deficiency of pseudocholinesterase. Perhaps as more case reports of delayed emergence from remifentanil arise, more research will be done on the esterases responsible for its breakdown, as well as deficiencies of those esterases.

Conclusion

At this time in the United States there are not many options for quick onset, short term paralysis apart from succinylcholine. In several countries rocuronium has replaced succinylcholine as it has a similar rate of onset and is completely, readily reversible with sugammadex. However, sugammadex is not currently available in the US. Similarly, in other countries mivacurium can be used as it also has a fairly rapid rate of onset and offset. Again, mivacurium is no longer available in the US. Thus, as the only short acting agent, the use of succinylcholine is inevitable in certain situations. As such, it is important that the possibility of undiagnosed pseudocholinesterase deficiency is entertained. More studies should be done on the use of FFP or whole blood in treating prolonged
Intraoperative diagnosis of Pseudocholinesterase deficiency paralysis after succinylcholine administration due to pseudocholinesterase deficiency.

With the growing use of neurophysiologic monitoring, it is important that anesthesiologists take into account the need for accurate measurements and the effects different medications have on monitoring. It is equally important to take into account the possibility of conditions such as pseudocholinesterase deficiency.

The loss of motor potentials in a case such as the one presented can be catastrophic. The surgeon may be unable to confidently perform the surgery and ensure proper placement of the pedicle screws. While SSEP monitoring can help approximate damage to the motor tract, there have been numerous reports of damage to motor tracts with no change in SSEP.
References


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² Train-of-four ³ Post-tetanic counts ² Second twitch


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References: