A Patient with Prolonged Paralysis

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CASE

A 19-year-old Asian male with no notable medical history presented to the emergency department with a 12-h history of acute abdominal pain. The patient’s condition was diagnosed as acute appendicitis, and he underwent an emergent laparoscopic appendectomy. A 1-mg dose of vecuronium followed by 120 mg of succinylcholine was administered to induce paralysis and facilitate endotracheal intubation.

The progression of the patient’s muscle relaxation was monitored intraoperatively with a train-of-four twitch monitor and was marked by fewer stimuli making it across the neuromuscular junction. In general surgeries, a neuromuscular block down to 2 twitches is adequate for rapid sequence induction. Normally, a dose of 0.5–2 mg succinylcholine per kilogram body weight completely abolishes the muscle response to nerve stimulation. Within 2 to 2.5 min, the neuromuscular junction starts to show signs of recovery, or twitches. In this case, the patient was administered 1.7 mg/kg succinylcholine. After the appendectomy was completed, however, the patient uncharacteristically remained paralyzed for 1.75 h. He showed no muscle twitches, no spontaneous inspiratory efforts, and no protective airway reflexes. He subsequently required sedation and assisted ventilatory support.

DISCUSSION

Cholinesterases are enzymes that catalyze the hydrolysis of choline esters. Acetylcholinesterase is distributed in the gray matter of the central nervous system, where it terminates synaptic transmission by specifically hydrolyzing the neurotransmitter acetylcholine (1, 2). Butyrylcholinesterase (BChE),⁴ also known as pseudocholinesterase, is distributed in the white matter of the central nervous system and in the blood. Although it has no known physiological func-

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QUESTIONS TO CONSIDER

1. What are the pharmacodynamic properties of succinylcholine?
2. What is the role of butyrylcholinesterase in the pharmacokinetics of succinylcholine?
3. What conditions can cause delayed recovery from succinylcholine administration?
4. What additional testing should be used to further evaluate this patient?

Succinylcholine, a neuromuscular blocking agent commonly used in surgical procedures to aid in endotracheal intubation, acts as a depolarizing neuromuscular blocker by mimicking the action of acetylcholine, thus generating an action potential at the motor end-plate. Succinylcholine has a half-life of 0.7 min and a volume of distribution of 0.02–0.04 L/kg. The action of succinylcholine is terminated by its diffusion away from the motor end-plate into the blood, where it is hydrolyzed by BChE (3). Normally, muscle function is restored approximately 10 min after discontinuation of the drug. Extended blockade with succinylcholine occurs in a subset of individuals who have BChE variants that either lack sufficient quantity of the enzyme or demonstrate a decreased affinity for substrate, thereby causing prolonged paralysis.

BChE is the product of the BCHE (butyrylcholinesterase) gene on chromosome 3 region 3q26. The gene consists of 73 kilobases in 4 exons separated by 3 introns (3). Mutations in the BCHE gene encode BChE protein products with varying reductions in activity that produce extended blockade and apnea in patients after exposure to succinylcholine. These genetically determined enzyme variants are characterized by decreased BChE production (quantitative variants) or by the production of dysfunctional
BChE molecules having decreased to no activity (qualitative variants) (2). BChE deficiency is often recognized only after an individual experiences unexpected periods of prolonged paralysis after succinylcholine administration.

A biochemical test from the 1950s for the phenotypic identification of BChE variants helped determine that the pharmacogenetic effect of BChE variants was familial (4–6). The test quantifies BChE enzyme activity in the serum in the presence and absence of the competitive inhibitor dibucaine, allowing the calculation of a “dibucaine number” (DN) that corresponds to the percentage of enzymatic inhibition: $\text{DN} = \frac{1}{\text{Total BChE activity}} \times 100$, where BChE activity is in units per liter. Together, the BChE activity and the DN can be used to determine an individual’s biochemical phenotype (Table 1).

With a prevalence of 96%, the most common phenotype is the usual (U) phenotype, which is characterized by a DN >80%. Individuals with this phenotype respond normally to succinylcholine administration with neuromuscular junction recovery achieved in approximately 10 min after exposure. In contrast, individuals with the atypical (A) phenotype have a DN <32% and experience prolonged paralysis after exposure to succinylcholine. A single allele at a frequency of 1 in 3000 is known to produce the A phenotype (4).

Three quantitative BChE variants have been described: James (J), Kalow (K), and Hammersmith (H). All have normal substrate binding activity but show decreased concentrations in the plasma (2). The slight decreases in BChE activity due to the quantitative variants do not usually cause a clinically important prolonged response to succinylcholine. These variants are more likely to affect the duration of response when present with other factors that influence BChE activity, such as a qualitative BChE variant, pregnancy, and anticholinesterase drugs (9).

**PATIENT FOLLOW-UP**

A blood sample was obtained for BChE activity and DN testing. The BChE activity was 57 U/L (reference interval, 3300–10 300 U/L) and the DN was <5% (reference interval, 83%–88%).

After a period of 4 h beyond the expected duration of succinylcholine action, the patient recovered his strength and met the criteria for extubation. He was discharged from the hospital 27.5 h after surgery. Because succinylcholine binds to the BChE active site, its presence in plasma will produce falsely decreased BChE activity and DN results. In the reported case, the initial BChE test was performed on a

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**Table 1. Characteristics associated with BChE phenotypes.**

<table>
<thead>
<tr>
<th>BChE phenotype</th>
<th>BChE activity, U/L</th>
<th>DN, %</th>
<th>Susceptibility</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>3300–10 300</td>
<td>83–88</td>
<td>None</td>
<td>96%</td>
</tr>
<tr>
<td>A</td>
<td>1600–4100</td>
<td>24–31</td>
<td>Very</td>
<td>1 in 3000</td>
</tr>
<tr>
<td>F</td>
<td>1600–4101</td>
<td>79–81</td>
<td>Somewhat</td>
<td>1 in 150 000</td>
</tr>
<tr>
<td>S</td>
<td>0–650</td>
<td>Any</td>
<td>Very</td>
<td>1 in 40 000</td>
</tr>
<tr>
<td>UA</td>
<td>1930–7300</td>
<td>72–79</td>
<td>Slightly</td>
<td>3%</td>
</tr>
<tr>
<td>UF</td>
<td>1260–5800</td>
<td>80–83</td>
<td>Slightly</td>
<td>Rare</td>
</tr>
<tr>
<td>US</td>
<td>1300–5100</td>
<td>83–87</td>
<td>Slightly</td>
<td>1 in 150</td>
</tr>
<tr>
<td>AS</td>
<td>540–1800</td>
<td>24–31</td>
<td>Very</td>
<td>1 in 8000</td>
</tr>
<tr>
<td>AF</td>
<td>800–3100</td>
<td>60–71</td>
<td>Somewhat</td>
<td>Rare</td>
</tr>
<tr>
<td>FS</td>
<td>1000–3800</td>
<td>78–84</td>
<td>Somewhat</td>
<td>Rare</td>
</tr>
</tbody>
</table>

* U, usual phenotype; A, atypical phenotype; F, fluoride-resistant phenotype; S, silent phenotype. Other phenotypes are heterozygous combinations of the U, A, F, and S phenotypes.
* Susceptibility to paralysis induced by neuromuscular blocking agents that require metabolism via BChE activity.
* Frequency of BChE phenotypes within the general population.
sample collected when succinylcholine was likely to be circulating in the patient’s blood. A repeat blood sample was obtained 8 days later for a repeat evaluation of the BChE activity and the DN; the results were 89 U/L and <5%, respectively. This BChE finding in conjunction with the low DN (<5%) suggested the patient had the S phenotype (Table 1). Knowledge of the phenotype is important because it will guide decisions regarding any future use of succinylcholine.

To better understand the genetic cause of the patient’s reduced BChE activity, we performed BCHE sequencing. PCR amplification of the 3 coding regions and intron/exon boundaries of the BCHE gene was

Fig. 1. BCHE sequencing results identifying a unique hemizygous/homozygous mutation: 1240 C>T (p.Arg414Cys, known as Arg386Cys) in exon 2.
performed with M13-tailed primers. Unincorporated primers and deoxyribonucleoside triphosphates were inactivated by incubating with ExoSAP (USB Corporation). Bidirectional DNA sequencing was performed with BigDye Terminator chemistry (Applied Biosystems) and M13 primers, and the product was analyzed on the ABI 3100 Genetic Analyzer (Applied Biosystems). Data were analyzed with Mutation Surveyor software (SoftGenetics) by comparing the generated sequence to a reference BCHE sequence (Genbank NC_000003.11).

BCHE sequencing identified a homozygous mutation: c.1240 C>T (p.Arg414Cys, known as Arg386Cys in the mature protein) in exon 2 (Fig. 1). This rare mutation has previously been reported only as a heterozygote and with an unknown clinical importance (10, 11). The case we have presented establishes that the BCHE Arg414Cys variant in the homozygous state produces prolonged paralysis upon exposure to succinylcholine, in agreement with an S phenotype. Arg414Cys is most likely a missense mutation causing inactivation of the BCHE active site.

Although the anesthesia community is aware that some individuals will have BCHE variants with reduced catalytic activity, BCHE and DN testing is infrequently performed, most likely because of the relatively low incidence of BCHE variants within the general population. Testing is frequently prompted when an individual experiences prolonged paralysis after exposure to succinylcholine, as occurred in this case. In this scenario, however, the timing of sample collection is important, and samples should be obtained only after all succinylcholine has completely cleared. Failure to do so can produce misleading results or uninterpretable biochemical data that could lead to an error, for example, in which the phenotype obtained implies no or only a slight risk of prolonged paralysis in an individual who is actually at high risk. In one study (12), 3 patients were assigned a BCHE phenotype of UF (slight risk), but 1 of the patients was determined to have an AA BCHE genotype (high risk) (12).

Because the half-life of succinylcholine is prolonged beyond the expected 0.7 min in patients with qualitative BCHE variants due to impaired catalytic activity, we recommend waiting a minimum of 48 h after succinylcholine exposure before collecting a sample for BCHE phenotyping.

For our patient, similar BCHE and DN results were obtained with 2 different samples, one of which was collected when succinylcholine was likely still present in the patient’s blood. The effect of succinylcholine on the BCHE and DN results was less apparent because the patient had a rare SS BCHE genotype, which produced a BCHE variant with very low catalytic activity.

**POINTS TO REMEMBER**

- Succinylcholine is a paralytic drug used to induce muscle relaxation and short-term paralysis.
- BCHE has no known physiological function but is capable of hydrolyzing exogenous choline esters found in certain drugs of abuse, aspirin, antidepressants, anti-convulsants, and paralytics.
- Extended paralysis by succinylcholine occurs in individuals with reduced BCHE activity due to genetically determined enzyme variants.
- Dibucaine is a competitive inhibitor of BCHE and is used to determine an individual’s DN, which is the percentage of BCHE inhibited by dibucaine.
- The BCHE activity and DN can be used to infer an individual’s biochemical BCHE phenotype.

**References**

Commentary

George Despotis*

In this Clinical Case Study by J.E. Whittington et al., the authors summarize the literature regarding butyrylcholinesterase (BChE) deficiency and provide a comprehensive summary of the various phenotypes in Table 1, which illustrates the relatively low frequencies of the atypical phenotypes of BChE. Nevertheless, there are substantial clinical implications of reduced BChE activity. Patients who have a low-activity BChE phenotype may experience serious complications if this genetic predisposition is not managed appropriately. Although the authors’ case illustrates the potentially serious implications of this disorder from a ventilatory perspective, the relative importance of reduced BChE activity on the pharmacokinetic and biologic activity of various other pharmacologic agents is also highlighted.

One issue not addressed in this Clinical Case Study is related to iatrogenic inhibition of this enzyme in the setting of either perioperative reversal of nondepolarizing muscle relaxant agents (e.g., neostigmine) or with the chronic management of myasthenia gravis (e.g., pyridostigmine). Although the prolonged duration of action of succinylcholine after the administration of agents like neostigmine has been extensively described, there are also a few reports of resistance to muscle relaxation with succinylcholine. One can speculate that patients with a hereditary reduction in BChE activity may display more-profound effects when these acetylcholinesterase inhibitors are administered. The clinical utility of recombinant (transgenic) BChE in these variant patients may also be of some benefit.

A better understanding of the issues outlined in this case should help clinicians confirm the diagnosis and help with the management of patients with reduced BChE when they are encountered in their clinical practice.

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Commentary

Roberta Goodall*

Prolonged paralysis due to low butyrylcholinesterase (BChE) activity after suxamethonium administration arises from either an inherited or an acquired deficiency, but the risk of prolonged paralysis is dependent on both enzyme activity and genotype. BCHE is a highly polymorphic gene, and the prevalences of the different mutations show the large geographic and ethnic variation. The terminology can be challenging (1). Biochem-

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