The implications of pseudocholinesterase in anesthesia
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Low levels of pseudocholinesterase have been determined to be a factor in prolonged paralysis after the administration of succinyldicholine. The author reviews the factors inherent to this condition and explores the anesthetic considerations necessary.

Prolonged paralysis following a single dose of succinyldicholine has been attributed to a low level of pseudocholinesterase in the plasma. Pseudocholinesterase, also known as plasma cholinesterase, is an enzyme formed in the liver, and its level may be reduced in liver disease, malnutrition, cachexia, and poisoning by organophosphorus compounds which are present in many nerve gases and insecticides.

In addition to low levels of pseudocholinesterase as a factor in prolonged paralysis after succinyldicholine, a similar prolonged response may be seen in patients with an abnormal or atypical pseudocholinesterase. This condition is known to be inherited. To further understand the implications of this enzyme to our use of depolarizing muscle relaxants and local anesthetics, we must first understand normal neuromuscular anatomy and transmission.

Basic to the understanding of cholinesterase is an understanding of the events at the neuromuscular junction during depolarization. The nerve fiber branches at its end to form the complicated structure called the end plate. The end plate invaginates into muscle fiber but lies entirely outside of the muscle fiber membrane. At the tips of the many nerve branches are sole feet. The invagination of the membrane is called the synaptic gutter, the space between the sole foot and fiber membrane is the synaptic cleft. At the bottom of the gutter are numerous folds which greatly increase the surface area at which the synaptic transmitter can act. In the sole foot, there are many mitochondria that synthesize the excitatory transmitter acetylcholine. Acetylcholine is stored in the sole foot in small vesicles. Around the rim of the synaptic gutter are large aggregates of the enzyme-true cholinesterase, also known as red cell cholinesterase.

As a motor nerve impulse reaches the nerve terminal some 50-100 vesicles of acetylcholine are released. It is believed that the nerve impulse causes calcium ions to move from extracellular fluid into the membranes of the sole feet, and that these ions, in turn, cause the vesicles of acetylcholine to rupture through the membrane. It has been found that in the absence of calcium, the release of acetylcholine is depressed. The positively charged acetylcholine migrates across the synaptic cleft and occupies an acetylcholine receptor near the membrane pore. When enough receptors are occupied by acetylcholine, the pores dilate and sodium ions rapidly enter the cell. The positively charged sodium ion is attracted to the interior of the cell by
the negative intracellular resting potential and by the low resting intracellular sodium concentration.

Potassium, in turn, leaves the muscle cell and transiently increases the potassium concentration in the extracellular fluid immediately surrounding the muscle. The interior of the cell then becomes positively charged. This process is called depolarization. The depolarization spreads to adjacent areas of the muscle membrane and, ultimately, the muscle fiber contracts. The acetylcholine receptor now has lost its negative charge and its affinity for acetylcholine. The acetylcholine is displaced and forms a substrate for true cholinesterase, which is found in abundance along the post-junctional membrane area. Water is added and the acetylcholine molecule is split into acetic acid and choline. These end products migrate back to the nerve terminal and are resynthesized by another enzyme, choline acetylase, to form more acetylcholine, which will be stored for further use.8

When acetylcholine is displaced from the receptor site, the pores constrict and sodium is removed from the cell by the sodium pump. Potassium then moves in a reciprocal fashion into the cell, and the cell is repolarized and ready for the next impulse. All of these events occur in a few milliseconds. The physiologic function of true cholinesterase, therefore, is to limit by hydrolysis the activity of acetylcholine which is released from the nerve terminal to produce a given muscular response. Anything that interferes with the depolarization-repolarization phase at the post-junctional membrane will cause neuromuscular block.8

Definition of cholinesterase

There are two types of cholinesterases found in the body, true or red cell cholinesterase and serum or pseudocholinesterase.1 The two can be distinguished by their distribution through the body. True cholinesterase was first described in 1935 and is basically found in nerves, muscles, and red cells. It is found at cholinergic synapses and myoneural junctions where it finds its preferred substrate—acetylcholine.2 This enzyme is inhibited by esters other than acetylcholine. It does not hydrolyze succinylcholine.4

Pseudocholinesterase, or serum cholinesterase, on the other hand, has little effect on acetylcholine at physiologic concentrations but will hydrolyze many other compounds, including succinylcholine.1 Pseudocholinesterase is found in the plasma, liver, brain, kidney, intestine, pancreas, and placenta. It is a mucoprotein formed in the liver and usually the serum contains 80-120 units. A level less than 25 is considered low. There is usually a high value in early childhood; and as age advances, the blood level falls. The pseudocholinesterase level is an indication of the functional reserve in the liver in chronic liver disease. A wide variety of inhaled and ingested esters form substrates for pseudocholinesterase, but its preferred substrates are long chain esters of choline. A number of drugs of interest to the anesthetist form substrates with pseudocholinesterase, including: procaine, Nesacaine®, tetracaine (Pontocaine®), and succinylcholine.1

Pseudocholinesterase is of special interest to the anesthetist because it is involved in the hydrolysis of both the succinyl esters of choline and the esters of benzoic acid, including procaine. “Procainesterase” is identical to pseudocholinesterase. Procaine has a stronger affinity for this enzyme than succinylcholine does, and therefore inhibits the hydrolysis of the relaxant. This is of particular importance if the two drugs are given together to a patient whose ability to metabolize succinylcholine is very much impaired.5

Succinylcholine’s properties of producing neuromuscular blockade were described in 1949, and soon thereafter, it was found that it was hydrolyzed by pseudocholinesterase.6 Succinylcholine produces a muscular paralysis of short duration and rapid onset. It acts by depolarizing the motor end-plate. It pre-
vents access of acetylcholine to the cholinergic receptors of the end plate and also influences the muscle fibers adjacent to the end plate, making them unexcitable.\textsuperscript{7}

Succinyldicholine is destroyed by hydrolysis at a rapid rate by pseudocholinesterase. This hydrolysis proceeds in two steps: the first, and rapid, step yields succinylmonocholine, and the second, and much slower, step breaks succinylmonocholine into succinic acid and choline. Since these two reactions occur at different rates, under physiological conditions, the dicholine is hydrolyzed six times faster than the monocholine, resulting in a temporary accumulation of monocholine. This compound has a neuromuscular blocking action of its own which is about 1/20 of the potency of dicholine in animals.\textsuperscript{2} In man, the potency of succinylmonocholine may be much closer to that of succinyldicholine.\textsuperscript{4}

Alkaline hydrolysis is a non-enzymatic process by which succinyldicholine can be hydrolyzed. Only 5\% of succinyldicholine per hour is destroyed in this manner, playing a small role in the destruction of this drug.\textsuperscript{5} In addition to the previously mentioned methods of hydrolysis, another enzyme has been identified that tends to increase the rate of destruction of succinyldicholine.\textsuperscript{2}

Anything that varies the serum cholinesterase level in the blood will modify either slightly or significantly the rate of hydrolysis of succinyldicholine. A high serum cholinesterase level is usually not a problem, and is found in obesity, patients with toxic goiters, nephrosis, psoriasis, alcoholism, and in depressed states with anxiety.\textsuperscript{10}

Causes of low levels

Low pseudocholinesterase may occur in conjunction with many different disease processes including: hyperpyrexia, cardiac failure, uremia, liver disease, malnutrition, severe anemia, second half of pregnancy, labor, and early postpartum days, following chemotherapy or radiation for carcinoma, hemodialysis, and after exposure to organic phosphorus insecticides.\textsuperscript{1} Pseudocholinesterase is produced in the liver, and the serum level is, therefore, most noticeably depressed in association with hepato-cellular damage.\textsuperscript{1} Pseudocholinesterase is also reduced, but to a lesser extent, in obstructive jaundice.

The seriousness of any clinical effect of pseudocholinesterase deficiency is inversely related to the serum level of the enzyme. In practice, it is not until enzyme activity is less than about 20-25 units/ml that any prolongation of block is noted; therefore, levels below 25 units/ml contraindicate the use of succinyldicholine in usual doses, though smaller doses can safely be used. If facilities are not available for this determination, some indirect evidence can be adduced from other liver function tests, particularly the serum albumin concentration.

The synthesis of serum albumin and pseudocholinesterase are closely related functions of the liver, and a low serum albumin concentration, in the absence of albuminuria, indicates that the serum pseudocholinesterase activity is also likely to be low. Raised transaminase levels are indicative of cellular necrosis and high values of hundreds or thousands of SGOT or SGPT units are also associated with parenchymatous liver damage. The serum level of pseudocholinesterase does not fall concurrently with the rise in transaminases, but only after a latent interval of about four days. In all borderline cases, it may be wiser to avoid succinyldicholine altogether, if other relaxants are an equally good choice.\textsuperscript{5}

Pseudocholinesterase is also reduced when there has been a protein depletion. Low values are found in starvation, and associated with malignant growths, particularly of the alimentary canal. Low levels have been found to be associated with most characteristically ill and debilitated individuals.\textsuperscript{1,5} One possible reason that prolonged apnea is not found more often in this type of patient is
their liability to receive a transfusion of blood or plasma preoperatively. One pint of stored blood contains enough enzyme to raise the serum level by about 5 units/ml.5

Pseudocholinesterase levels slightly below normal have been reported in persons exposed to certain insecticides containing organophosphorous compounds. These levels probably would not be associated with any clinical difficulties with succinylcholine. A severe depletion of pseudocholinesterase activity is associated with ingestion of these compounds, which may be done during an attempted suicide. This also follows exposure to nerve gases, but the clinical picture in such cases is dominated by the inhibition of true cholinesterase in the central nervous system. These patients will most likely require assisted ventilation, and the use of succinylcholine to facilitate intubation would be contraindicated, according to some but not all anesthetists.

It has also been shown that there can be a decrease in pseudocholinesterase activity in patients receiving Cytoxan®. Wang and Ross (1963) have shown by in vivo and in vitro studies that this drug is a potent cholinesterase inhibitor. A single dose of 0.5-1 gm depressed the serum pseudocholinesterase activity to about 30% of its previous level. In patients treated with Cytoxan® the depressed activity persisted for about 30-40 days after the drug was withdrawn. Preoperative pseudocholinesterase levels should be performed on any patient who has recently received this drug, or any related compound, if the use of muscle relaxants is contemplated.11

Discovery of two enzymes

The enzymatic hydrolysis of succinylcholine in man is now well understood. Nevertheless, anesthetists occasionally still encounter cases where the patient exhibits a prolonged response to the drug. Originally, it was believed that all of these cases could be accounted for by the diminished production of pseudocholinesterase in the liver, or by any of the previously discussed reasons for a decreased serum concentration. However, not all of the patients appeared to be suffering from malnutrition or liver damage; in fact, many of the cases of prolonged apnea occurred in very fit, healthy young patients.

This puzzle was resolved when Kalow and Davis discovered in 1958 that in man there are at least two types of plasma pseudocholinesterase enzymes—a normal and an atypical one.1,2 Apparently individuals could lead perfectly normal lives with either of these enzymes, and it was only when they received their first injection of succinylcholine that any differentiation could be made.

The physiologic difference between these two enzymes is one of peculiar activity. The normal enzyme functions at any concentration of succinylcholine in the blood, even at relatively low levels; whereas, the abnormal enzyme is only effective at high blood levels of succinylcholine. Therefore, if a patient with abnormal pseudocholinesterase receives a dose of succinylcholine, the dilution of the substrate (brought about through rapidly mixing with the blood volume) yields a drop in its concentration below the effective level for the atypical esterase.

Immediately after the administration of succinylcholine, the pseudocholinesterase begins its hydrolysis. This action is complete before the drug reaches the motor end plate and, therefore, before the actual action of the drug. After reaching the motor end plate, the process of diffusion completes the hydrolysis of succinylcholine. If succinylcholine is given to an individual with abnormal pseudocholinesterase, he is unable to hydrolyze the drug before the large quantities reach the motor end plate. With these extremely large amounts of succinylcholine at the end plates, the diffusion process takes a long period of time; hence, there is a prolonged period of apnea.12

In order to properly diagnose the
presence of a genetic variation, a cholinesterase test should be performed. In clinical practice a simple test paper, Alchotest, is used, and has been found to be reasonably accurate. This method will give an estimation of the total amount of enzyme in the blood, but is unable to differentiate between the typical and atypical enzyme. Fortunately, the patients with only atypical enzymes in their blood give low values for these tests. However, there are a number of people with a mixture or some normal and some abnormal enzymes who have values just on the low side of normal. For this reason, a low pseudocholinesterase value may be due to two causes: liver damage as a result of disease and malnutrition, or the presence of an atypical enzyme.

To differentiate between these two causes requires a special test. Kalow and Genest demonstrated in 1957 that these two conditions—normal pseudocholinesterase and the presence of an atypical enzyme—behave differently when the local anesthetic dibucaine is added to the serum. The presence of atypical pseudocholinesterase is due to the inheritance of an abnormal gene. The dibucaine test has been devised to detect the possible genotype of the deficiency. The purpose of this test is to examine the amount of inhibition of a particular serum by dibucaine.

Typical pseudocholinesterase hydrolyzes most substrates rapidly, but is inhibited 30% or more when dibucaine is introduced. Atypical pseudocholinesterase hydrolyzes most substrates slowly, but is inhibited very little by dibucaine—20% or less. The percentage of inhibition is referred to as the dibucaine number. An individual with a dibucaine number of 70 or more would be considered a normal homozygote. He would have two normal genes. A person with a dibucaine number of 40-50 would fall into the intermediate group and would probably be a heterozygote. He would be carrying one normal and one abnormal gene. A person with a dibucaine number of 20 or less would be considered a homozygote, producing only the atypical enzyme. In other words, both of his genes would be abnormal.

On the basis of Kalow's studies in 1959, it was found that 96.2% of the population is normal, having two similar normal genes. These people can destroy succinyldicholine very rapidly. A small percentage of the population, 3.8%, was found to have a mixture of genes—one normal and one abnormal—making them heterozygotes. They destroy succinyldicholine also, but far less efficiently, so that the duration of action of the succinyldicholine may be slightly prolonged by 5-10 minutes. In only one of 2,800 individuals was there a homozygotic atypical condition, unable to hydrolyze succinyldicholine.

Patients with a low dibucaine number also have a low pseudocholinesterase, but the inverse is not necessarily true. A patient with malnutrition or liver disease may have a low pseudocholinesterase level, yet have a normal dibucaine number.

Studies done in 1961 by Harris and Whittaker found that sodium fluoride could be used instead of dibucaine. In comparing the results of the two methods, they noticed that a few patients had normal dibucaine numbers but had abnormally low fluoride numbers. Then they suggested that there was yet another gene for pseudocholinesterase. The homozygote for the fluoride gene has been found to have a moderately prolonged response to succinyldicholine.

More studies during 1962 by Liddell, using the dibucaine test, found evidence of yet another gene, the "silent" gene, which can occupy a position on one or both chromosomes in a similar fashion as does the typical or atypical gene. This gene fails to elaborate any pseudocholinesterase at all. In this condition, the patient shows a severely prolonged response to succinyldicholine. Any patient who has inherited a combination of the "silent" gene and any other of the abnormal genes would, although he is heterozygous, also be markedly succinyldicholine sensitive.
since he has no “normal” enzyme in his serum.\textsuperscript{14}

It is evident, therefore, that there are at least four genes for pseudocholinesterase—the normal, the dibucaine resistant, the fluoride resistant, and the silent gene. These can combine to form ten genotypes, of which six are associated with a markedly increased sensitivity to succinylcholine. It is estimated that one of these six will appear in every 1,500 patients.\textsuperscript{10} It is apparent that most heterozygous individuals who have a fair amount of normal enzymes are unlikely to give rise to any clinical difficulty unless the total enzyme activity is concurrently reduced by one of the previously mentioned disease processes. Since the incidence of this is one in 25, the anesthetist must give succinylcholine to several of these patients every month without being aware of it.\textsuperscript{10}

**Anesthetic considerations**

As has been previously stated, the duration of apnea of a single dose of 0.5-1.0 mg of succinylcholine is 2-4 minutes, and any apnea lasting longer than 10 minutes is considered abnormal. Often, the cause of failure of return of respiration is not related to the relaxant at all, but to sedation, the depression of the respiratory center, or hyperventilation. The diagnosis of prolonged response to succinylcholine must, therefore, be made using the peripheral nerve stimulator. This instrument, when applied to a peripheral nerve, will indicate both the degree of block present and the characteristics of that block. If after 10 minutes of apnea, the hand muscles are still completely paralyzed, it is safe to say that the patient is experiencing a prolonged response to succinylcholine. A prolonged response to succinylcholine may occur for one of three reasons: low or atypical pseudocholinesterase, overdose of the drug, or long term anti-cholinesterase therapy, as in glaucoma.\textsuperscript{2}

The fact that succinylcholine changes its characteristics from one of depolarization to one resembling non-depolarization is now well documented. Because the patients with atypical pseudocholinesterase have large volumes of succinylcholine circulating, they frequently show the characteristics of a desensitization block. The presence of the signs of a non-depolarizing-type block might tempt some to use an anticholinesterase to reverse the block.

It should be understood that the term “non-depolarization” in this case is used loosely, because the block differs from that produced by curare in many ways. First, unlike curare, the membrane potential does not remain unchanged at the resting level of 60-90 mV. Secondly, evidence has been found that succinylcholine penetrates the interior of the muscle fibers at about the same time that the non-depolarizing characteristics appear, which curare does not do. Thirdly, and most importantly, a further dose of succinylcholine antagonizes a curare block, but potentiates a desensitization block.\textsuperscript{15}

In clinical practice, the use of anticholinesterase drugs in the treatment of desensitization block has led to much confusion, since sometimes it improves the situation, and other times, it has prolonged the apnea even further. The reason for this discrepancy depends upon the presence or absence of succinylcholine in the circulation when the antagonist is given. If the succinylcholine has all been hydrolyzed, then the block will reverse. On the other hand, if there is still some succinylcholine present, the breakdown process will be slowed even further. Also, large doses of anticholinesterase drugs act as depolarizing agents in their own right, which will also increase the neuromuscular blockade.\textsuperscript{15}

Any apnea prolonged more than 15 minutes following the administration of a minimal or reasonable dose of succinylcholine should arouse suspicion concerning the possible presence of atypical pseudocholinesterase, and a blood sample should be drawn to determine the dibucaine number. This result can give you an unequivocal diagnosis,
but takes a fair amount of time; furthermore, few institutions are set up to determine dibucaine numbers. A strong presumptive diagnosis can be made with a peripheral nerve stimulator. This will rule out apnea caused by hyperventilation.

The most important factor in the treatment of these patients is ventilation. Patience and care must be taken so that the patient is ventilated properly throughout the entire period of apnea. The flow rates should be carefully chosen within the physiologic range for the patient. All narcotics should be antagonized so that there is no confusion with narcosis. Diaphragmatic movement is usually the first indication of returning muscle tone. If a patient is overventilated while paralyzed, the feeble initial respiratory efforts do not occur as soon as they would normally, and the duration of paralysis is greatly extended. It is obvious, therefore, that a respirameter is a very necessary tool, along with the peripheral nerve stimulator, in diagnosing and treating this problem.14

Many other treatments for this problem are in use. Some anesthetists encourage the use of drugs to stimulate urinary excretion of the succinylcholine, while others recommend the use of 400-800 ml of double strength plasma, given as fast as the circulatory condition of the patient allows.2 A concentrated solution of pseudocholinesterase has also been produced in the hope of reducing the length of time it takes for a patient with atypical pseudocholines- terase to recover.17 The results of these treatments have been disappointing. It has been found that, even without any of these treatments, complete recovery occurs, usually within 4 hours.

After any narcotic used has been antagonized, and the major effects of any anesthetic agent used has worn off, the patient may still lie paralyzed and frightened. It is recommended by some that a nitrous oxide/oxygen mixture18 be maintained so that the patient is not as aware of his surroundings, and that amnesia is preserved.5

Apart from the immediate management of the apnea, the anesthetist has a great moral responsibility to the patient and his relatives. Any apnea of more than 15 minutes duration after a single dose of succinylidicholine for which no other reasonable explanation can be offered should be regarded as a clue to a possible instance of inherited pseudocholinesterase abnormality, and the appropriate investigations should be carried out both on the patient and on the immediate relatives. When abnormal homozygotes or "silent" heterozygotes are detected, the family physician and all individuals involved should be informed of the problem so that a similar event will not occur in the future.

REFERENCES
(9) Katz, Ronald, unpublished data.

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