Notes 1: Atypical Pseudocholinesterase, Malignant Hyperthermia & Succinylcholine

- **Drug**: Succinylcholine (example)
- **Drug Class**: Skeletal Muscle Relaxant (blocks transmission on the muscle side of the NMJ)
- **Pharmacokinetics**: Succinylcholine’s action is terminated following its metabolism by cholinesterase & pseudo-cholinesterase.
- **Atypical Pseudocholinesterase**:
  - Succinylcholine should be used carefully in patients with reduced plasma cholinesterase (pseudo-cholinesterase) activity.
  - *Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase* (e.g., patients heterozygous or homozygous for atypical plasma cholinesterase gene).
  - Patients homozygous for atypical plasma cholinesterase gene (1 in 2,500 patients) are extremely sensitive to the neuromuscular blocking effect of succinylcholine. The atypical enzyme has a ~100 fold lower affinity for substrate compared to the normal enzyme. In these patients, a 5-to 10-mg test dose of succinylcholine may be administered to evaluate sensitivity to succinylcholine, or neuromuscular blockade may be produced by the cautious administration of a 1-mg/mL solution of succinylcholine by slow IV infusion.
  - Apnea or prolonged muscle paralysis should be treated with controlled respiration.
- **Side Effects**: adverse reactions to succinylcholine consist primarily of an extension of its pharmacological actions. Succinylcholine causes profound muscle relaxation resulting in respiratory depression to the point of apnea; this effect may be prolonged.
- **Dibucaine test**: a test that can be used to identify patients with an abnormal ability to metabolize succinylcholine. Under standardized conditions, a dose of dibucaine (an inhibitor of pseudocholinesterase) will inhibit the normal enzyme by ~80%, as compared to 20-25% in patients homozygous for the atypical enzyme, and by 40-70% in patients heterozygous for the atypical enzyme. The percent inhibition is referred to as the "dibucaine number". 1 in 3000 patients have atypical pseudocholinesterase.
- **NOTE**: Malignant Hyperthermia (a topic to be discussed later on during this course): can also be triggered by succinylcholine or volatile general anesthetics in
individuals having a heterogenetic disorder unrelated to abnormalities in plasma cholinesterase (1 in 10,000 patients).

Reference:

- rxlist.com - Succinylcholine (Anectine ®)

http://tmedweb.tulane.edu/pharmwiki/doku.php/atypical_pseudocholinesterase

**Notes 2: Pseudocholinesterase or plasmacholineesterase or butylcholinesterase**

- Enzyme of the liver and plasma
- Little or not present in the NM junction
Drugs metabolised

- Succinylcholine
- Mivacurium
- Ester group of LA
- Esmolol
- Remifentanil

Conditions where levels are decreased

- Pregnancy
- Malignancy
- Malnutrition
- Collagen vascular disease
- CRF
- Hypothyroidism
- Liver disease
- Drugs like OCP, MAO inhibitors, ecothiophate, cytotoxic drugs, anticholineesterase drugs, hexafluorenium, Metachlorpramide, bambuterol, esmolol
- Burns

Pseudocholinesterase deficiency results in delayed metabolism of only a few compounds of clinical significance, including the following: succinylcholine, mivacurium, procaine, and cocaine. Of these, its most clinically important substrate is the depolarizing neuromuscular blocking agent, succinylcholine, which the pseudocholinesterase enzyme hydrolyzes to succinylmonocholine and then to succinic acid.

In individuals with normal plasma levels of normally functioning pseudocholinesterase enzyme, hydrolysis and inactivation of approximately 90-95% of an intravenous dose of succinylcholine occurs before it reaches the neuromuscular junction. The remaining 5-10% of the succinylcholine dose acts as an acetylcholine receptor agonist at the neuromuscular junction, causing prolonged depolarization of the postsynaptic junction of the motor-end plate. This depolarization initially triggers fasciculation of skeletal muscle. As a result of prolonged depolarization, endogenous acetylcholine released from the presynaptic membrane of the motor neuron does not produce any additional change in membrane potential after binding to its receptor on the myocyte. Flaccid paralysis of skeletal muscles develops within 1 minute. In normal subjects, skeletal muscle function returns to normal approximately 5 minutes after a single bolus injection of succinylcholine as it passively diffuses away from the neuromuscular junction. Pseudocholinesterase deficiency can result in higher levels of intact succinylcholine molecules reaching receptors in the neuromuscular junction, causing the duration of paralytic effect to continue for as long as 8 hours. This condition is recognized clinically when paralysis of the respiratory and other skeletal muscles fails to spontaneously resolve.
after succinylcholine is administered as an adjunctive paralytic agent during anesthesia procedures. In such cases respiratory assistance is required.

In 2008, an experimental new drug was discovered for the potential treatment of cocaine abuse and overdose based on the pseudocholiesterase structure. It was shown to remove cocaine from the body 2000 times as fast as the natural form of BChE. Studies in rats have shown that the drug prevented convulsions and death when administered cocaine overdoses. This enzyme also metabolizes succinylcholine which accounts for its rapid degradation in the liver and plasma. There may be genetic variability in the kinetics of this enzyme that can lead to prolonged muscle blockade and potentially dangerous respiratory depression that needs to be treated with assisted ventilation.

Mutant alleles at the BCHE locus are responsible for suxamethonium sensitivity. Homozygous persons sustain prolonged apnea after administration of the muscle relaxant suxamethonium in connection with surgical anesthesia. The activity of pseudocholinesterase in the serum is low and its substrate behavior is atypical. In the absence of the relaxant, the homozygote is at no known disadvantage.

Finally, pseudocholinesterase metabolism of procaine results in formation of paraaminobenzoic acid (PABA). If the patient receiving procaine is on sulfonamide antibiotics such as bactrim the antibiotic effect will be antagonized by providing a new source of PABA to the microbe for subsequent synthesis of folic acid.

http://nishurs.blogspot.com/2011/05/pseudocholinesterase-or.html