Cholinesterases and the Dibucaine Number

There are two types of cholinesterases: acetylcholinesterase, ("true" cholinesterase), which is found in red blood cells and nervous tissue, and pseudocholinesterase which is found in plasma and many other tissues. True cholinesterase is used by the red blood cell in its energy utilization processes and to conserve the sodium/potassium ion gradient. It is most likely produced while the red blood cell is still immature. In nervous tissue, there is probably a dynamic equilibrium of production and destruction of the enzyme.

Pseudocholinesterase is synthesized in the liver. Its circulating plasma concentration is affected by the functional integrity of the liver and by genetic factors. In liver disease serum pseudocholinesterase levels are depressed.

The site of the physiological function of true cholinesterase is at the neuromuscular junction. Acetylcholine production in this junction permits the nerve impulse to pass through the motor endplate of the nerve fiber and trigger muscle action. True cholinesterase depolarizes the motor endplate junction by hydrolyzing acetylcholine and thus allowing the nerve cell to transmit another impulse later in time. If the enzyme is poisoned and cannot function, the axonal junction cannot be depolarized and no further impulses can be carried along the nerve sheath, resulting in a loss of muscular control. The effects are due to an accumulation of acetylcholine. These effects can be reversed by blockers of acetylcholine receptors or blockers of the anti-cholinesterase poison.

Anticholinesterase materials are used as pesticides, nerve gases, and muscle relaxants (physostigmine and neostigmine). Pesticides such as parathion, malathion, and diisopropyl fluorophosphate are absorbable via percutaneous routes, inhalation, and GI ingestion. They reversibly bind to acetylcholinesterase and inhibit the enzyme from performing its normal hydrolytic action at the synaptic junction. The acute symptoms of organophosphorus poisoning show multiple organ effects. Ocular symptoms include miosis, conjunctival congestion, brow ache, and watery nasal discharge. Respiratory symptoms include tightness and wheezing due to bronchoconstriction and increased bronchial secretions. GI symptoms include anorexia, nausea, vomiting, cramps and diarrhea. With percutaneous absorption, localized sweating and muscular fasiculation may occur.

Pseudocholinesterase is a glycoprotein which is part of the alpha-2 globulin fraction and which is synthesized by the liver. Its physiological function is largely unknown. It does, however, hydrolyze the neuromuscular blocking agent, succinylcholine to succinic acid and choline. Adequate activity of this enzyme is required to allow recovery from the effects of succinylcholine. The genetic control of the synthesis of plasma cholinesterase is governed by a gene which may be present in at least four co-dominant forms: E_1^u the usual gene, E_1^a the atypical gene, E_1^f the fluoride resistant gene, and E_1^s the "silent" gene.

Various studies have established the frequencies of occurrence for the possible combinations of allelic types. $E_1^uE_1^u$ occurred in 97.2% of 563 dental students screened in Detroit during the years 1963 to 1970. The genotypic combination $E_1^uE_1^a$ occurred in 2.1%. $E_1^uE_1^f$ occurred in 0.7%. A study of a British population of 780 students yielded a similar distribution of 96.4% with the usual genotype and 3.1% of the $E_1^uE_1^a$ genotype. $E_1^aE_1^a$ occurred in about 0.035% or 1/2800 of the population.

The vulnerable types with respect to prolonged apnea following succinylcholine administration are

$E_1^a E_1^a = A$ $E_1^a E_1^s = AS$ $E_1^s E_1^s = S$

$E_1^f E_1^f = F$ $E_1^a E_1^f = AF$ $E_1^f E_1^s = FS$

These represent less than 0.1% of the population. Dibucaine inhibition can be used to differentiate phenotypes A and AS from U and UA. In this test, pseudo-cholinesterase is incubated with dibucaine (nupercaine hydrochloride). U is inhibited to the extent of about 80% while A and AS are inhibited to about 20%. The dibucaine number is given as the percent inhibition and may range from 0 to 100. Fluoride inhibition can be used to identify the F genotype.

The following table shows the percent inhibition by dibucaine for the various phenotypic expressions of the enzyme:

Phenotype	Percent Inhibition by Dibucaine
U	83.6 ± 2.6
A	19.9 ± 5.4
AS	20.7 ± 8.2
S_1	5.3 ± 8.6
S_2	67.6 ± 8.6
F	71.8 ± ?
AF	60.2 ± 6.2
FS	76.7 ± ?
UA	72.7 ± 6.2
UF	79.8 ± 2.4
US	84.4 ± 1.6

Since the incidence of the unusual phenotypes is such a small percentage of the population, it is infeasible to screen patients presurgically for sensitivity to succinylcholine. However when a patient exhibits prolonged apnea following surgery, a dibucaine number should be obtained. The test need not be done as a stat procedure since the level of the enzyme remains the same, within narrow limits, throughout life. It is not affected by the presence of succinylcholine. If the dibucaine number indicates that the patient has one of the abnormal phenotypes, it would be wise to have siblings of the affected patient and children, if any, tested to ascertain if they are carriers of the abnormal gene. This information can limit the possibility of anyone having to needlessly suffer through an apneic episode following the administration of succinylcholine.