PSEUDOCHOLINESTERASE ACTIVITY: DETERMINATION AND INTERPRETATION IN PEDIATRIC ANESTHESIA

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Pseudocholinesterase (PChE), also known as plasma cholinesterase, is a serine hydrolase capable of hydrolyzing esters including acetylcholine, succinylcholine, mivacurium and ester type local anesthetics such as procaine, chloroprocaine, tetracaine, cocaine and heroin. PChE is synthesized by the liver, and is found in the plasma, the pancreas, the heart and the brain. It has a serum half life of 8 to 12 days, and is an alpha 2 globulin, a tetramer of 342000 molecular weight, that exists in aggregate form.

Two types of serum cholinesterase exist: a normal and an atypical variety. Both types are gene transmitted. The gene coding for pseudocholinesterase is situated on chromosome 3. About 95% of the population carry only the normal esterase (homozygous), about 4% a mixture of both enzymes (heterozygous), and about 1 in 2800 (0.04%) only the atypical esterase (homozygous). The most frequent mutation corresponds to the phenotype A. The mutation is of an adenine to a guanine and transform the codon GAT to GGT, with a resultant synthesis of a glycocolle instead of an aspartic acid. The substitution of an acid amino acid (aspartic acid) by a neutral amino acid (glycocolle) accounts for the decrease in affinity of the enzyme for the cholinesters. Low pseudocholinesterase level may mean a reduced amount of the normal enzyme or the presence of the atypical enzyme in varying amounts.

The qualitative tests dibucaine number (DN) and fluoride number

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(FN) reflect reduction in PChCE resulting from the addition of dibucaine or sodium fluoride to the assay. Atypical variants were originally described by Kalow, who identified individuals whose PChCE could not metabolize succinylcholine but was only partially inhibited by dibucaine. Dibucaine (Nupercaine), a local anesthetic, will inhibit the activity of the normal enzyme to a greater extent than the atypical one, irrespective of the actual plasma levels of either. It inhibits normal pseudocholinesterase activity by 80%, but inhibits the homozygous atypical enzyme by only 20%. The heterozygous enzyme is characterized by an intermediate 40-60% inhibition. The percentage of inhibition of pseudocholinesterase activity is termed the dibucaine number. The dibucaine number in proportional to pseudocholinesterase function and is independent of the amount of enzyme. Therefore adequacy of pseudocholinesterase can be determined in the laboratory quantitatively in units per liter and qualitatively by the dibucaine number.

The amount of PChE is age dependent under normal circumstances. At birth, the activity is low compared with 50% of non pregnant adults. There is complete disagreement about PChE activity following that age. According to earlier workers there is a dramatic increase in the activity during the first 3 weeks of life to a value greater than that of the healthy adult and which persists until the third year. The later workers report that the activity remains at about 50% of the adult value until 6 months and no particular interest seems to have been paid to the next 2.5 years of life. In fact, there are no established norms until the age of 3 years. Between 3 and 6 years the mean PChE activity of 1024 children is about 30% above the adult level but begins to decrease during the fifth year and continues to do so until the adult level is reached at puberty.

In addition to the previous data, there is more documentation in the literature about variations occurring according to age and sex. Lepage et al., in a study of 3372 subjects, with approximately equal numbers of each sex, and where 29% were children aged 4 to 14 years, described that in males, cholinesterase activity was not significantly correlated with age. In females, there was a significant correlation with age; cholinesterase activities (50th percentile) decreased significantly by approximately 14%
from 10-15 to 15-25 years (p <0.001) and reached a minimal value of 5500 (SD 1400) U/L between 25 and 35 years. Sexual maturation affected cholinesterase activity in females. The value for cholinesterase activity for percentiles 25, 50 and 97.5 were significantly lower (p <0.01) by about 10% in girls between 10 and 14 who had reached menarche than in girls of the same age who had not. The use of estrogen-containing oral contraceptives results also in a significant decrease in plasma cholinesterase.

Clinically, in infants and children, the shorter duration of mivacurium may lead to the assumption that pseudocholinesterase activity is higher at this age than in adults. In fact, the results of several studies are conflicting. Investigators have administered mivacurium by continuous infusion to children and examined factors influencing the infusion rate to maintain certain degrees of twitch depression. Alifimoff and Goudsouzian reported no statistical association between the mivacurium infusion rates in children and the activity of plasma cholinesterase (pseudocholinesterase). In contrast, Brandom et al. reported that mivacurium infusion rates in children were influenced by both plasma cholinesterase activity and age. Finally, Meretoja and Olkkola reported that from 1 to 15 years old, there was a negative correlation between the mivacurium infusion rates and the age of children. In another study, Markakis et al. showed that in children, IR$_{50}$ (Infusion rate producing 50% twitch depression) increased with plasma cholinesterase activity but did not vary with (log) age, IR$_{90}$ (Infusion rate producing 90% twitch depression) was not related to plasma cholinesterase activity or age. There was no relationship between plasma cholinesterase activity and (log) age. IR$_{50}$ values in children were approximately twice those in adults with comparable plasma cholinesterase activity. Only 22% of the variation in mivacurium infusion rates was a function of the variation in plasma cholinesterase activity. The authors suggested that there is more variability in either mivacurium’s pharmacokinetics or pharmacodynamics (or both) in children than in adults, and concluded in a later study, that maturational changes in mivacurium’s clearance and neuromuscular junction sensitivity to
mivacurium may be responsible for the variability with different infusion rates.

The review of the literature as described above would suggest some discrepancy between the values of pseudocholinesterase activity in children and adults. However, the laboratory measurements results of pseudocholinesterase activity are not correlated to the age or sex factor. In fact, there is no study establishing the norms from age 6 months to 3 years.

In fact, several limitations to genotyping by biochemical methods exist: First, biochemical testing cannot distinguish between primary and secondary pseudocholinesterase deficiency, the latter caused by drugs, hepatic disease, pregnancy, and carcinomas, and second, several reports emphasise the lack of precision and accuracy with biochemical determination of pseudocholinesterase activity, especially in newborns and infants.\textsuperscript{3,22-26}

The identification of a single gene locus encoding for pseudocholinesterase on chromosome 3q26 allowed molecular genetic techniques to be used for diagnosis in patients with reduced pseudocholinesterase activity.\textsuperscript{27,28} A variety of mutation responsible for most variants has been published\textsuperscript{29,30}. Recently, these molecular genetic methods have been applied and are the most appropriate available techniques for genotyping. Despite limited data describing the relation between clinical data, i.e., duration of neuromuscular block by succinylcholine, biochemical analyses, and molecular genetic investigations, the determination of pseudocholinesterase genotypes has shown that within a population, there is a high prevalence of pseudocholinesterase sequence variations, especially the allele frequency of 0.128 of the K variant.\textsuperscript{31} This variability would explain the difficulty of defining an optimal individual dose of succinylcholine for induction of anesthesia.\textsuperscript{32-34}
References