Apnea in an Atypical-fluoride Resistant (E₁⁺E₄⁻) Heterozygote for Serum Cholinesterase

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Interest in the enzyme cholinesterase (E.C. 3.1.1.8) in serum was initiated by its pharmacogenetic relationship to the muscle relaxant, succinylcholine, which is hydrolyzed normally by the usual form of this enzyme. Subsequent study has identified at least four alleles at the E₁ locus: the usual (E₁⁺), the atypical (E₁⁻), the fluoride resistant (E₁⁺), and the silent gene, or genes (E₁⁻); and another variant (C₄⁻) at a second locus, E₂. Individuals possessing the homozygous form or combinations of these unusual variants of serum cholinesterase manifest differing degrees of sensitivity to succinylcholine. Table 1 classifies the various phenotypic combinations with which cases of prolonged muscular paralysis and apnea following the administration of customary amounts of succinylcholine or less have been reported.

We have recently observed prolonged muscular paralysis and apnea in a young child heterozygous for the atypical and fluoride resistant genes (E₁⁺E₁⁻), which confirms the susceptibility of persons with this rare phenotype to possible anesthetic hazard from succinylcholine. In addition, our findings suggest that there is no age difference or dependency to this hazard, and underscore the benefit of preoperative screening for the detection of unusual cholinesterase phenotypes and decreased levels of cholinesterase activity. Individuals thus identified would be protected from unnecessary anesthetic complications; a card or bracelet identifying their problem would provide notification should they need future anesthesia.

**REPORT OF A CASE**

A 3½-year-old Caucasian boy with a history of recurrent tonsillitis, mouth breathing, and questionably decreased hearing ability was admitted to the hospital for tonsillectomy in March 1972. Physical examination disclosed no abnormality except tonsillar hypertrophy and moderate cervical adenopathy. Urinalysis and complete blood count were normal, and a sweat chloride evaluation for cystic fibrosis was normal. Preoperatively, seco-bartal, 40 mg. and atropine, 0.2 mg. were given im. Anesthesia was induced with halothane, nitrous oxide, and oxygen, after which the child was given succinylcholine, 20 mg. iv, to facilitate endotracheal intubation. He made no effort to breathe spontaneously for 25 minutes following intubation. During the period of apnea, a sample of the patient's blood was sent to our laboratory for assay of the cholinesterase enzyme.

The patient was genotyped as heterozygous for atypical and fluoride-resistant genes (E₁⁺E₁⁻), with an activity of 3.88 (normal range 2.5-5.5). Since he is an adopted child, pedigree data for his family are unavailable.

**METHODS AND MATERIALS**

Plasma cholinesterase activity was determined utilizing butyrylthiocholine iodide, 2.0 mM, as substrate in Tris buffer, 0.05 M, pH 7.3 at 25 C. All samples were tested for atypical and fluoride variants employing methods reported from this laboratory4,5 in which sodium fluoride is used as differential inhibitor in Tris and phosphate buffers with butyrylthiocholine as substrate. Inhibition values, Tris buffer plus NaF versus phosphate buffer plus NaF, were plotted two-dimensionally, and each variant was identified by its position on a graph.5

**DISCUSSION**

It is now accepted that the fluoride-resistant gene is allelic, with normal, atypical, and silent genes at the same locus. However, because of previous lack of information about serum cholinesterase variants and the rarity of the fluoride allele,6 few individuals with this allele have reportedly experienced apnea.7,10 Improved methodology for differentiation of cholinesterase variants now permits rapid, simple, and more accurate ascertainment of genotype using very small amounts of blood.5,11
CLINICAL WORKSHOP

Table 1. Genotypes Determined by Known Serum Cholinesterase Genes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Succinylcholine Sensitivity*</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Homozygotes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E₁⁺E₁⁺</td>
<td>Not sensitive</td>
<td>This genotype is found in about 97 per cent of Caucasians and in most Negroes.</td>
</tr>
<tr>
<td>E₁⁺E₁⁻</td>
<td>Markedly sensitive</td>
<td>Frequency of the E₁⁻ allele about 15-30 x 10⁻² in Caucasians. The E₁⁻ allele is rare, with an estimated frequency of 1 x 10⁻²; however, it is unusually common in Western Alaska, where 48 of the 64 reported cases originated.</td>
</tr>
<tr>
<td>E₁⁻E₁⁻</td>
<td>Markedly sensitive</td>
<td></td>
</tr>
<tr>
<td>E₁⁻E₁⁻</td>
<td>Moderately sensitive</td>
<td></td>
</tr>
<tr>
<td>Heterozygotes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E₁⁺E₁⁻</td>
<td>Not sensitive</td>
<td></td>
</tr>
<tr>
<td>E₁⁺E₁⁻</td>
<td>Not sensitive</td>
<td></td>
</tr>
<tr>
<td>E₁⁻E₁⁻</td>
<td>Markedly sensitive</td>
<td></td>
</tr>
<tr>
<td>E₁⁺E₁⁻</td>
<td>Moderately sensitive</td>
<td>Recommendations 8, 12</td>
</tr>
<tr>
<td>E₁⁻E₁⁻</td>
<td>Moderately sensitive</td>
<td>Reference: 10</td>
</tr>
</tbody>
</table>

* In all instances reported as not sensitive individuals with these genotypes have been described. Marked sensitivity here indicative of potential apnea in excess of two hours from a standard dose of succinylcholine. Moderate sensitivity is considered potential apnea lasting 20 minutes to an hour.

In addition to the prolonged respiratory assistance and general supportive care often necessitated by succinylcholine sensitivity, additional hazards of pulmonary infection and cardiac arrest in such individuals have been reported. Because of cost and logistic factors within most hospitals, the feasibility of preoperative screening of patients who are to receive succinylcholine remains controversial. Since most patients reacting untowardly to this drug are homozygous atypical, testing is generally directed toward identifying this variant alone.

Recent improvement in methodology has resulted in easier identification of the fluoride-resistant variant, and a number of samples previously identified as heterozygous atypical, E₁⁺E₁⁻, are now being correctly typed as atypical fluoride-resistant, E₁⁺E₁⁻. However, unlike procedures for detecting the atypical allele, E₁⁻, additional, more skillful testing is necessary for positive identification of the fluoride-resistant allele, E₁⁻. Most hospitals, even large ones, are unable or unwilling to provide this service for anesthesiologists. Also, most hospitals that offer cholinesterase assays report only levels of enzymic activity. These results cannot be used to identify the various genotypes and are insufficient for family pedigree studies.

Mass preoperative screening for cholinesterase genotype is considered too costly by most hospital laboratories, many of which have only a few postsurgical samples referred to them per year. Two possible ways to solve this complex problem are: 1) provide commercially packaged, easily employed, assay procedures to measure activity and to identify the various genotypes; 2) establish regional cholinesterase research units, as described by Whittaker and Vickers. These investigators offered to anesthesiologists of the United Kingdom a service of cholinesterase activity determination and genotyping of any samples from individuals developing prolonged apnea during surgery. By using a standard methodology, Whittaker and Vickers hoped to prevent erroneous genotyping and to insure that family studies were not rendered less valuable by doubts as to exact results. The cost of this simple, specialized assay (activity plus genotyping) is estimated to be five to ten dollars per sample.

Had only generally available methods been used to test the serum of the patient reported, results would have been interpreted as indicative of the presence of the E₁⁺E₁⁻ genotype. Since such individuals are not exquisitely sensitive to succinylcholine, some other explanation would have been sought for the prolonged episode of apnea, and the patient...
would have run the risk of receiving the medication on another occasion. This case stresses the importance of thorough investigation and complete genotypic classification of an individual who has experienced apnea or prolonged muscular paralysis associated with administration of succinylcholine. Correct information regarding succinylcholine-sensitive individuals and subsequent family follow-up studies warrant this expense in order to preclude further exposure and risk to the patient or to other susceptible family members.

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REFERENCES


Drug-induced Heat Stroke

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Malignant hyperthermia is not the only thermoregulatory disorder which may require the attention of the anesthetist. Drug-induced “heat stroke” is not uncommon, and its treatment may necessitate emergency airway management and intensive care. Awareness of this cause of heat stroke is necessary for proper management. Two patients recently admitted to San Francisco General Hospital during

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“heat spells” in which ambient temperatures exceeded 90 F illustrate the problems in treatment.

REPORT OF TWO CASES

Patient 1. A 48-year-old Negro man was brought to the emergency room after having collapsed on the street. He was deeply comatose, and no history was immediately available. His skin was hot and dry. Physical examination of the chest disclosed no abnormality, and there were no focal neurologic signs. The blood pressure was 180/120 torr, pulse 120/min, and respirations 50/min. Rectal and axillary temperatures were above 108 F. Ventilation was 60 l/min. Arterial blood gas values with the patient breathing