SUXAMETHONIUM SENSITIVITY

A Family Study

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SUMMARY: A case of sensitivity to suxamethonium is described. Investigation of her immediate family enabled them to be reassured that they have only a minimal risk of exhibiting similar sensitivity.

Introduction

Suxamethonium, a depolarising muscle relaxant, was introduced into anaesthetic practice in 1951. Its action is normally rapidly terminated due to its destruction by an enzyme present in plasma—cholinesterase (acetylcholine acylhydrolase, E.C. 3.1.1.8.). Soon after its introduction cases were described where the drug had a prolonged action (Evans et al 1952). These patients had an abnormally low cholinesterase level due, usually, to an inherited defect. They appeared to have an abnormal recessive gene present and were homozygous. Heterozygous individuals had cholinesterase levels overlapping the normal and abnormal (low) plasma concentrations.

Kalow (1960) showed that the cholinesterase of normal plasma was inhibited more strongly by many cholinesterase inhibitors than was that of the atypical cholinesterase. One inhibitor which produced a marked difference was the local anaesthetic dibucaine. Kalow and Genest (1957) called the percentage inhibition produced by a fixed concentration of dibucaine under standard conditions the dibucaine number (DN). The DN differentiates three groups of individuals; the normal homozygote with a DN of less than 80, atypical homozygote DN less than 20 and the heterozygote DN 45-69.

Subsequently it has been realised that further atypical cholinesterases can be identified. Harris and Whittaker (1961) described the fluoride-resistant enzyme. They defined the percentage inhibition produced by a fixed concentration of sodium fluoride under standard conditions as the fluoride number (FN).

Liddell, Lehmann and Silk (1962) found a patient with marked sensitivity to suxamethonium who had no detectable cholinesterase activity. Family data showed this again to be inherited. The patient was shown to be a homozygote with 2 "Silent genes". This gene is an allele of other cholinesterase variants. (Simpson and Kalow, 1964).

Increased cholinesterase activity has been described in a group of individuals who possess a very slow moving fifth band of cholinesterase activity when normal serum is separated by gel electrophoresis. The presence of this C_5 band is genetically determined. This variant is not an allele of the other atypical variants but is determined at another locus (Harris et al 1963). Individuals having this electrophoretic variant do not appear to be sensitive to suxamethonium.

These recognised variants of cholinesterase probably represent only a fraction of the possible genetic variants of the enzyme. At present the five well established cholinesterase genes are noted usually by the nomenclature proposed by Motulsky (1964) using the symbol E for esterase. There are two cholinesterase loci E_1 and E_2 . Four variants

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occur at the first locus:— E_1^u —the usual gene, E_1^a —the atypical dibucaine-resistant gene, E_1^f —the atypical fluoride-resistant gene, E_1^s —the silent gene.

Only two variants are known at the second locus:—

E_2^- —the usual gene, E_2^+ —the C_5 variant.

The biochemical characteristics, frequency and sensitivity to suxamethonium of the genotypes at the first locus are shown in Table I. (Lehmann and Liddell, 1969).

Table I
The biochemical characteristics, frequency and suxamethonium sensitivity of the genotypes at the E_1 locus

Genotype	Dibucaine number	Fluoride number	Frequency in a British population	Suxamethonium sensitivity
Homozygotes				
$E_1^u E_1^u$	77—83	57—68	Normal population	?1 in 3,200 moderately sensitive
$E_1^a E_1^a$	15—25	20—25	1 in 2,800	All markedly sensitive
$E_1^f E_1^f$	64—67	34—35	?1 in 300,000	?All moderately sensitive
$E_1^s E_1^s$	—	—	?1 in 140,000	All markedly sensitive
Heterozygotes				
$E_1^u E_1^a$	52—69	42—55	1 in 26	?1 in 500 moderately sensitive
$E_1^u E_1^f$	71—78	50—55	?1 in 280	?1 in 200 moderately sensitive
$E_1^u E_1^s$	77—83	57—68	?1 in 190	Not known; ?1 in 500 moderately sensitive
$E_1^a E_1^f$	47—53	31—39	?1 in 29,000	?All markedly sensitive
$E_1^a E_1^s$	15—25	20—25	?1 in 20,000	All markedly sensitive
$E_1^f E_1^s$	64—67	34—35	?1 in 200,000	?All moderately sensitive

This paper reports a further individual with an abnormal response to suxamethonium and the results of an investigation into her family. An assessment is made of the risk of suxamethonium sensitivity in future members of her family.

Case history

In July 1971, Mrs. S. H. was anaesthetised for an evacuation of her uterus following an incomplete abortion. Following premedication with atropine, anaesthesia was induced with thiopentone. Intubation was performed after suxamethonium (50 mg). Anaesthesia was maintained with N_2O/O_2 with positive pressure ventilation and supplemented with pentazocine (15 mg I.V.). At the end of the procedure (10 minutes), no sign of return of muscle power could be demonstrated although, in the absence of a nerve stimulator, it could only be surmised that there may be a defect in neuromuscular conduction. The patient was ventilated with 50:50 N_2O/O_2 until spontaneous muscle activity returned three hours later.

At the return of adequate muscle power she was extubated, after which she had a normal postoperative recovery with complete amnesia for the whole period.

Investigation.

Postoperatively, investigation of the patient's serum revealed low cholinesterase activity and her dibucaine number was compatible with her being homozygous for the atypical cholinesterase variant $E_1^a E_1^a$. Further specimens of serum from her and twenty-four of her twenty-eight living close relations were investigated by the Cholinesterase Research Unit, Chemistry Department, University of Exeter, Devon.

The results, shown in Table 2, demonstrate that she is the only member of her

Table II
The biochemical characteristics of the family arranged according to genotype

Genotype	Number	Cholinesterase activity	Dibucaine number	Fluoride number
Normal		80—120u	77—83	57—68
Propositus $E_1^a E_1^a$	III 7	42	21	20
Heterozygotes	I 4 II 4 II 5 II 6 II 7 III 8 III 12 III 13 IV 3	62 58 79 71 73 65 76 70 104	64 64 62 63 63 68 64 64 64	46 44 45 48 48 49 53 50 47
Homozygotes	I 3 II 1 II 2 II 8 III 1 III 4 III 6 III 9 III 10 III 11 III 14 III 15 III 16 III 17 IV 1	76 126 108 87 146 78 76 103 112 100 104 108 115 102 136	80 79 81 79 80 80 82 82 82 82 82 82 80 80 80	63 58 61 56 63 62 62 62 58 60 60 58 62 57 60

family to be homozygous for the atypical dibucaine resistant gene. Nine other members of the family are heterozygous. The family tree has been constructed in Fig. 1.

Discussion

In 1968 Whittaker and Vickers initiated the Cholinesterase Research Unit. This unit estimates cholinesterase activity, and dibucaine and fluoride numbers. A standard methodology is used to prevent erroneous genotyping.

Apnoea following anaesthesia is a common problem. When it is suspected that the cause may be due to an atypical cholinesterase, then it is essential that the patient's

Fig. 1. Family tree of suxamethonium sensitive family.

cholinesterase genotype is determined. If the results are abnormal it is incumbent upon the anaesthetist both to warn the other members of the family and also to determine their genotype so that their risk during or after a possible future anaesthetic is reduced.

This study has enabled us to reassure the other members of the propositus' family that they run minimal risk of being sensitive to suxamethonium. However, as the incidence of the heterozygote $E_1^a E_1^u$ is 1:26 and of the other heterozygotes $E_1^f E_1^u$ and $E_1^s E_1^u$ are respectively 1:280 and 1:190, the risk of heterozygotes of this family marrying another heterozygote is 1:22. There is thus a 1:88 chance that a heterozygote of this family will produce a suxamethonium sensitive child.

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