On the identification and frequency of the J and K cholinesterase phenotypes in a Caucasian population

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SUMMARY An analysis of investigations performed between December 1978 and September 1982 into the cholinesterase status of 795 Caucasian patients has revealed an $E_1^aE_1^j$ genotype in three (0.4%) and an $E_1^aE_1^k$ genotype in 22 (2.8%). Both groups of patients are at increased risk of sensitivity to suxamethonium. Inhibitor numbers characteristic of these genotypes are reported which it is hoped will assist other workers to identify them more easily.

While the J allele is probably rare among the general population it is suggested that as many as one person in 76 could be a KK homozygote.

Our findings provide a possible explanation of the low cholinesterase activities seen in some patients for which there is no other obvious cause.

Soon after succinyl dicholine (suxamethonium, Scoline) was introduced as a short acting muscle relaxant in 1951 it became apparent that some persons were unusually sensitive to its effects, experiencing muscular paralysis which lasted for several hours instead of the more usual 2 to 4 minutes. While it was suspected that an abnormality of serum cholinesterase (acyl choline acyl hydrolase E.C.3.1.1.8) was responsible for this sensitivity, it was not until 1957 that Kalow and Genest¹ first described the atypical cholinesterase variant and provided a biochemical basis for the clinical observation. Unlike the usual enzyme form, atypical cholinesterase is unable to hydrolyse succinyl choline at pharmacological concentrations.² Kalow's work stimulated the search for other cholinesterase phenotypes culminating in the recognition of the fluoride resistant allele in 1961³ and the silent allele, which is associated with little or no enzyme activity, in 1962.⁴

That other phenotypes may occur has since been suggested by Whittaker following use of chloride⁵ and n-butanol⁶ as inhibitors, but her observations await confirmation.

In 1976 Garry *et al*⁷ identified a quantitative cholinesterase variant which they called the J phenotype. Two years later Rubinstein *et al*⁸ described the K phenotype, so named in honour of Werner Kalow. Their work was confirmed in Leeds using slightly different techniques.⁹

The J and K phenotypes, which are associated with reductions in measured enzyme activity of approximately 66% and 33% respectively, are unusual in that they can be identified with certainty only when they occur together with the atypical variant. In such combination $E_1^aE_1^j$ and $E_1^aE_1^k$ give rise to characteristic inhibitor numbers.

This report outlines our experience of the frequency of the J and K variants in a Caucasian population since we first recognised them in 1978.

Methods

Cholinesterase activities were measured according to the method of Evans and Wroe and are based upon the hydrolysis of propionyl thiocholine at 25°C.¹⁰

Establishment of enzyme genotype has relied upon the degree of inhibition of benzoyl choline hydrolysis using dibucaine,¹ fluoride,³ and the dimethyl carbamate of (2-hydroxy-5-phenyl-benzyl) trimethylammonium bromide (Ro 02-0683).¹¹

All measurements were made using an SP 1800 recording spectrophotometer (Pye Unicam Instruments, Cambridge).

Results

From December 1978 to September 1982, 795 specimens were analysed for cholinesterase status in this laboratory. Most blood samples derived from patients in whom prolonged muscular paralysis was suspected following treatment with suxamethonium

TABLE Distribution of 795 specimens of serum according to cholinesterase genotype together with inhibitor numbers used for their identification.

Genotype	Number identified 7.12.78-21.9.82	(%)	Range of activities associated with each genotype (U/ml)	Range of inhibitor numbers associated with each genotype		
				Dibucaine	Fluoride	Ro 02-0683
$E_1^uE_1^u$	476	(60)	2.1-8.6	80-83.5	57-63.5	93.5-97.5
$E_1^uE_1^a$	169	(21.3)	2.1-6.1	58-68	45.5-53	66.5-80
$E_1^aE_1^a$	67	(8.4)	0.66-2.1	13.5-27	17-31.5	5-22.5
$E_1^uE_1^f$	15	(1.9)	3.0-6.4	72-81	41.5-56.5	91-100
$E_1^aE_1^f$	7	(0.9)	0.79-3.4	43-52	27-36.5	58-69
$E_1^uE_1^s$	19	(2.4)	1.2-5.3	77-84	51-67.5	94.5-99
$E_1^fE_1^s$	3	(0.4)	1.25-2.4	61.5-70	30-43	92.5-100
$E_1^aE_1^s$	6	(0.8)	0.2-0.95	14.5-26	21-32.5	4.5-28.5
$E_1^aE_1^k$	22	(2.8)	0.98-3.7	47.5-58	33-48	49-66.5
$E_1^aE_1^j$	3	(0.4)	1.05-2.4	40-46.5	35.5-39	40-48.5
$E_1^jE_1^k$	1	(0.1)	2.2	82	63	97.5
$E_1^sE_1^s$	1	(0.1)	—	—	—	—
$E_1^uE_1^k$	6	(0.8)	3.45-5.55	77.5-82	59-63	94.5-97

or their immediate families. The majority of patients lived within the Yorkshire region, for which a routine analytical service is provided, but a number came from elsewhere in the United Kingdom and Europe. The distribution of these specimens according to genotype is shown in the table.

Discussion

During the 4-year period covered by this survey, only three patients have been shown to be hetero-

zygous for both the A and J cholinesterase forms. This is the same number as those we have found to be heterozygous for the fluoride resistant and silent variants who are reported to occur with a frequency of 1 in 150 000.¹² There is no doubt, therefore, that the J phenotype is rare, but nevertheless the identification of $E_1^aE_1^j$ patients should not prove difficult if laboratories are prepared to look seriously for them, especially if Ro 02-0683 numbers are determined,

FIG 1 Cholinesterase activities measured on $E_1^uE_1^a$ and $E_1^aE_1^k$ heterozygotes.

FIG 2 Dibucaine numbers measured on $E_1^uE_1^a$ and $E_1^aE_1^k$ heterozygotes.

since these are particularly valuable in establishing this combination (table). All patients with an $E_1^a E_1^j$ genotype are likely to be suxamethonium sensitive and have been warned accordingly. Owing to the similarity of dibucaine and fluoride numbers, there is some risk of $E_1^a E_1^j$ patients being incorrectly labelled $E_1^a E_1^f$ by those laboratories which use only these two inhibitors. However, the failure to find evidence for the fluoride resistant gene in the parents of such subjects should lead to a strong suspicion of an $E_1^a E_1^j$ ascription.

In contrast to $E_1^a E_1^j$, we have found patients who are $E_1^a E_1^k$ to be relatively common and suspect that they may frequently be incorrectly typed as $E_1^u E_1^a$ owing to the similarity of inhibitor numbers. Enzyme activities, dibucaine, fluoride, and Ro 02-0683 inhibitor numbers for the two genetic combinations (figs 1 to 4) illustrate the small, but significant, differences between them. In this laboratory, patients who are shown to be $E_1^u E_1^a$ heterozygotes are not considered to be at great risk of suxamethonium sensitivity except during pregnancy, when women experience a physiological fall in cholinesterase activity. This may be of sufficient

FIG 3 Fluoride numbers measured on $E_1^u E_1^a$ and $E_1^a E_1^k$ heterozygotes.

FIG 4 Ro 02-0683 numbers measured on $E_1^u E_1^a$ and $E_1^a E_1^k$ heterozygotes.

magnitude to result in a prolongation of relaxation time should they be exposed to suxamethonium during the course of their delivery.¹³ $E_1^a E_1^k$ heterozygotes have a mean activity even lower than that of $E_1^u E_1^a$ patients and therefore the risk of susceptibility to suxamethonium is correspondingly increased. Of the 22 cases described here, five had activities of less than 2.0 U/ml which, in our experience, puts them at risk of prolonged apnoea, while three had activities of less than 1.7 U/ml, below which we regard suxamethonium sensitivity as probable. It is therefore of more than academic interest that a laboratory intending to give a cholinesterase service should be able to identify these persons with certainty.

The Kalow variant cannot be recognised when in combination with the usual enzyme, since inhibitor numbers for $E_1^u E_1^k$ and $E_1^u E_1^u$ patients are identical.⁹ Nevertheless, in the six obligatory $E_1^u E_1^k$ patients seen in this laboratory, the mean cholinesterase activity was observed to be 4.4 U/ml, in contrast to

5.5 U/ml in a population of young healthy subjects who were phenotypically usual and to whom an $E_1^uE_1^u$ genotype has been ascribed. This observation is in accordance with the findings of Rubinstein *et al.*⁸ However, we have also shown the K allele to be present in 11.5% of patients likely to be labelled $E_1^uE_1^a$, giving a gene frequency of 0.115 since selection is on the basis of the possession of one atypical gene. If our patients are typical of heterozygotes elsewhere, then it is probable that the gene will occur with a similar frequency throughout the population. If this is so, one person in 76 will be expected to be an $E_1^kE_1^k$ homozygote. This could be one explanation for the low activities observed from time to time in healthy patients whose enzyme is otherwise normal, as judged by current biochemical criteria. However, techniques other than the use of inhibitors may be required before this hypothesis can be tested further. We hope that our experience will encourage other laboratories to analyse their results in more detail; the findings on patients who have previously been difficult to type may then be explained on the basis of the presence of the J or K variants.

References

- ¹ Kalow W, Genest K. A method for the detection of atypical forms of human serum cholinesterase: determination of dibucaine numbers. *Can J Biochem Physiol* 1957;**35**:339–46.
- ² Kalow W. The distribution, destruction and elimination of muscle relaxants. *Anaesthesiology* 1959;**20**:505–18.
- ³ Harris H, Whittaker M. Differential inhibition of human serum cholinesterase with fluoride: recognition of two new phenotypes. *Nature* 1961;**191**:496–8.
- ⁴ Liddell J, Lehmann H, Silk E. A 'silent' pseudocholinesterase gene. *Nature* 1962;**193**:561–2.
- ⁵ Whittaker M. The pseudocholinesterase variants. Differentiation by means of sodium chloride. *Acta Genet Stat Med (Basel)* 1968;**18**:556–62.
- ⁶ Whittaker M. Differential inhibition of human serum cholinesterase with n butyl alcohol: recognition of new phenotypes. *Acta Genet Stat Med (Basel)* 1968;**18**:335–40.
- ⁷ Garry PJ, Dietz AA, Lubrano T, Ford PC, James K, Rubinstein HM. New allele at cholinesterase locus 1. *J Med Genet* 1976;**13**:38–42.
- ⁸ Rubinstein HM, Dietz AA, Lubrano T. E_1^k , another quantitative variant at cholinesterase locus 1. *J Med Genet* 1978;**15**:27–9.
- ⁹ Evans RT, Iqbal J, Dietz AA, *et al.* A family segregating for E_1^j and E_1^k at cholinesterase locus 1. *J Med Genet* 1980;**17**:464–7.
- ¹⁰ Evans RT, Wroe J. Is serum cholinesterase activity a predictor of succinyl choline sensitivity? An assessment of four methods. *Clin Chem* 1978;**24**:1762–6.
- ¹¹ Liddell J, Newman GE, Brown DF. A pseudocholinesterase variant in human tissues. *Nature* 1963;**198**:1090–1.
- ¹² Whittaker M. Plasma cholinesterase variants and the anaesthetist. *Anaesthesia* 1980;**35**:174–97.
- ¹³ Evans RT, Wroe J. Plasma cholinesterase changes during pregnancy. Their interpretation as a cause of suxamethonium-induced apnoea. *Anaesthesia* 1980;**35**:651–4.

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