Apnoea following suxamethonium: the genetic study of four generations of a family

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SUMMARY Nineteen subjects were investigated as a result of apnoea following the administration of suxamethonium occurring in one member of the family. Examination of the blood for cholinesterase activity, dibucaine number, and fluoride number was carried out and the appropriate genotype determined. The significance of the genetic variation of plasma cholinesterase in relation to suxamethonium apnoea is discussed. Five subjects had the genotype $E_1^aE_1^a$, seven were of genotype $E_1^aE_1^s$, three were $E_1^sE_1^s$, and four $E_1^aE_1^s$. Nine members of the family were considered to be at risk for the administration of suxamethonium. The appropriate action to safeguard other members of the family following a case of apnoea is outlined. By routine preoperative blood examination, 92 of 100 cases of suxamethonium apnoea resulting from a genetic abnormality of plasma cholinesterase can be anticipated.

Suxamethonium (succinylcholine, Scoline), a depolarising neuromuscular blocking agent, is widely used as a short acting muscular relaxant. It is hydrolysed by the enzyme acylcholine acylhydrolase with the code number E.C.3.1.1.8, commonly known as plasma cholinesterase (ChE). The average adult dose of 1 mg/kg body weight produces respiratory paralysis by peripheral action of two to four minutes' duration. A period of apnoea lasting more than 10 minutes is considered abnormal.

Before incriminating a genetic abnormality of ChE, apnoea of central origin, or resulting from the anaesthetic agent or technique, or certain antibiotics,^{1,2} or abdominal surgery itself,³ have to be excluded. Moreover various diseases and drugs can affect ChE.⁴

The following case illustrates the latent hazard which every anaesthetist fears when, following suxamethonium used routinely and in a single dose in a fit person during the course of a normal operating list, apnoea occurred as a result of a genetic abnormality of the ChE.

Case report

A housewife aged 50, weighing 53 kg, was admitted to hospital for a D and C, curettage and cauterisation of the cervix. Premedication was an intramuscular injection of pethidine 50 mg and atropine 0.6 mg.

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Sleep was induced with 100 mg methohexitone sodium intravenously followed by intravenous injection of 100 mg suxamethonium chloride. After intubation anaesthesia was maintained with nitrous oxide-oxygen (5 : 3 l/m) and 0.5 to 1.0% halothane. Apnoea persisted for 90 minutes despite ventilation with 5 to 6 l/m oxygen and full respiration did not return for a further 30 minutes. A peripheral nerve stimulator was not available. Blood gas analysis carried out half an hour after apnoea showed a pH of 7.05, P_{CO_2} 12.5 kPa (94 mmHg), P_{O_2} 28.1 kPa (211 mmHg), plasma bicarbonate 22.9 mmol/l, base excess -10 mmol/l. One hour later when recovery was taking place the values were pH 7.32, P_{CO_2} 6.0 kPa (44 mmHg), P_{O_2} 20.0 kPa (150 mmHg), plasma bicarbonate 19 mmol/l, base excess -6 mmol/l. The plasma cholinesterase, as repeated after discharge, was 22 units, the dibucaine number 18, and fluoride number 17.

As a result of the suxamethonium apnoea and the associated abnormal ChE the author decided to examine the blood of other members of the family. Nineteen out of a possible 21 (I.2 was not alive) were investigated. IV.2 (aged 11 months) and II.6 were not examined.

Methods

ChE activity ($100 \times$ change in pH in one hour) was estimated with benzoylcholine as substrate using the

ultraviolet spectrophotometer.⁵ The differential inhibition by dibucaine hydrochloride⁶ and sodium fluoride⁷ enabled the dibucaine number (DN) and fluoride number (FN) to be determined.

Results

The figure sets out the relationship of the members of the family to the proband, together with their genotypes. Table 1 shows the cholinesterase activity, details of the inhibition studies, genotypes, and suxamethonium sensitivity for each of the members tested. It will be seen that of the 19 subjects examined nine were considered to be sensitive to suxamethonium.

Discussion

Although the blood gas analysis showed that the patient was inadequately ventilated, the primary cause of the prolonged apnoea was considered to be a genetic abnormality of the cholinesterase.

There are four allelic genes of importance to the anaesthetist which control ChE activity and which function at the same locus, designated E_1 using the nomenclature of Motulsky.⁸ These are the usual E_1^u , the dibucaine resistant or atypical E_1^s ,⁹ the fluoride resistant E_1^f ,^{7 10-12} and the silent gene E_1^i .¹³ They give rise to ten genotypes whose characteristics are given in table 2, based on the work of Whittaker on a cross-section of the British population.⁴ It will be seen that six of the genotypes are associated with a distinctly increased sensitivity to suxamethonium.

The estimation of the DN and FN enables recognition of groups containing the genes E_1^u , E_1^f , and E_1^i , but not E_1^s , as heterozygotes with the silent gene have the same DN and FN as the homozygous phenotype. Its presence may be suspected when the ChE activity is below that which would be expected for the corresponding homozygote, but confirmation requires family studies. Thus, in table 1, II·3 and III·4 are of genotype $E_1^u E_1^s$ not $E_1^u E_1^u$, and similarly II·1, II·5, II·7,

FIGURE Family pedigree.

TABLE 1 Plasma cholinesterase activity, dibucaine and fluoride number, genotype, and suxamethonium activity for each member examined as shown in the figure

Subject	Sex	Age	Plasma cholinesterase	DN	FN	Genotype	Suxamethonium sensitivity
I·1	F	74	101	65	50	$E_1^u E_1^u$	No
II·1 (proband)	F	50	22	18	17	$E_1^u E_1^s$	Yes
II·2	M	53	99	84	60	$E_1^u E_1^u$	No
II·3	F	46	57	81	60	$E_1^u E_1^s$	Yes
II·4	M	49	75	61	48	$E_1^u E_1^s$	Probably not
II·5	F	47	21	24	21	$E_1^u E_1^s$	Yes
II·7	M	43	34	22	19	$E_1^u E_1^s$	Yes
III·1	M	25	22	63	45	$E_1^u E_1^s$	Yes
III·2	M	21	26	22	26	$E_1^u E_1^s$	Yes
III·3	F	23	89	82	62	$E_1^u E_1^u$	No
III·4	M	19	46	80	57	$E_1^u E_1^s$	Yes
III·5	M	18	81	78	58	$E_1^u E_1^s$ (probable)	Probably not
III·6	M	15	80	66	49	$E_1^u E_1^s$	Probably not
III·7	M	14	132	83	61	$E_1^u E_1^u$	No
III·8	F	28	48	63	48	$E_1^u E_1^s$	Yes
III·9	M	30	129	82	58	$E_1^u E_1^s$	No
III·10	M	27	104	67	48	$E_1^u E_1^s$	No
III·11	M	11	81	82	60	$E_1^u E_1^s$ (probable)	Probably not
IV·1	F	5	101	63	45	$E_1^u E_1^s$	Yes, especially if pregnant

TABLE 2 Distribution, suxamethonium sensitivity, and biochemical characteristics of plasma cholinesterase variants in a British population.

Genotype	Group	Relative mean enzyme activity	Dibucaine No		Fluoride No		Frequency	Suxamethonium sensitivity
			Mean	Range	Mean	Range		
$E_1^u E_1^u$	Usual 'U'	100	80	77-83	61	56-68	96%	? 1 in 2500 moderately sensitive
$E_1^u E_1^s$		70	80	77-83	61	56-68	1 in 190	? 1 in 1000 moderately sensitive
$E_1^s E_1^f$	Fluoride resistant 'U ₁ '	86	74	70-83	52	46-54	1 in 200	? 1 in 100 moderately sensitive
$E_1^s E_1^i$	Intermediate 'I'	77	62	48-69	50	44-54	1 in 25	? 1 in 500 moderately sensitive
$E_1^s E_1^f$	Fluoride resistant 'I ₁ '	59	53	45-59	33	28-39	1 in 20 000	All moderately sensitive
$E_1^f E_1^f$	Homozygous fluoride resistant	74	67	64-69	36	34-43	1 in 154 000	All moderately sensitive
$E_1^f E_1^s$		37	67	64-69	36	34-43	1 in 150 000	All moderately sensitive
$E_1^f E_1^a$	Dibucaine resistant or atypical 'A'	43	21	8-28	19	10-28	1 in 2000	All very sensitive
$E_1^f E_1^s$		22	21	8-28	19	10-28	1 in 29 000	All very sensitive
$E_1^f E_1^f$	Homozygous silent variant	Enzyme activity nil or too low to measure					1 in 100 000	All very sensitive

and III·2 are not $E_1^a E_1^a$ but $E_1^a E_1^s$. These latter subjects demonstrate the general rule that those with a low DN have a low ChE. The converse, however, is not necessarily true as is seen in the case of II·3 and III·4.

Not all genotypes $E_1^u E_1^s$ have a low ChE, as pointed out by Liddell *et al.*¹³ and as is seen in III·11. It is not unusual in this type of heterozygosity for one gene to do the work of almost two.

Those subjects designated 'probably not' in table 1 are males. Had they been females they would have been issued with cholinesterase warning cards, as there can be at least a 25% drop in the ChE during pregnancy and early postpartum period.¹⁴

Seven members of the family are of genotype $E_1^u E_1^a$. Subjects with this phenotype are issued with a warning card if they are females and premenopausal, irrespective of their ChE level, or if they are males with a ChE of less than 50% of the usual group.⁴ This practice differs from that in Denmark where all subjects with an abnormal genotype are issued with a warning card.¹⁵

IV·1, aged 5, is considered at risk not only because she is female and heterozygous, but because at this age the ChE is about 35% above the adult level^{16 17} so that her present adequate level (101) will decrease over the next 7 to 8 years.

In the case of IV·2, a female child aged 11 months, blood examination is being postponed until the age of 5. In the meantime, since it is known that at birth the ChE is low,¹⁸⁻²¹ the parents and the general practitioner were advised that suxamethonium should be avoided, as suxamethonium apnoea in infancy, although rare, has been recorded.²² This child is genetically at risk because of the possibility of having an abnormal genotype $E_1^u E_1^a$, as the parents (III·8 and III·9) are $E_1^u E_1^a$ and $E_1^u E_1^u$, and is also liable to have a low ChE because one of the parents (III·8) has a ChE of only 48 and this

reduced ChE activity can be transmitted independently.

Five subjects are of normal genotype $E_1 E_1^u$ with adequate ChE and are therefore considered not to be sensitive to suxamethonium. It is important to bear in mind that some subjects show sensitivity to suxamethonium even though they fall in the normal group and have normal enzyme activity.^{4 15} This anomaly has so far not been satisfactorily explained.

Berry and Whittaker²³ showed that 13% of relatives of those sensitive to suxamethonium were themselves sensitive. In this study, the figure is nearer 50% because of the preponderance of the silent gene (seven out of 19 members). For the same reason the high incidence of apnoea because of the silent gene (six out of nine cases) contrasts with the low incidence of 1% in Whittaker's review of over 1000 cases of suxamethonium sensitive subjects.⁴ The preponderance of the silent gene in this family study is the result of I·2, the father of the proband and no longer alive, being almost certainly of genotype $E_1^f E_1^s$. This can be deduced in accordance with simple Mendelian inheritance because the offspring of I·1 and I·2 (II·1, II·3, II·5, and II·7) all possess the silent gene and I·1 does not.

As a result of this family study, each subject at risk was issued with a warning card of suxamethonium sensitivity by the Cholinesterase Research Unit. In addition they also wear a bracelet or necklace with a disc upon which is inscribed in contrast colour "No Scoline". Their general practitioners were also informed.

The occurrence of suxamethonium apnoea in clinical practice is estimated at 1 in 2400 cases.²⁴ Since the incidence of apnoea as a result of a genetic abnormality of the cholinesterase is 1 in 1500,²⁵ and that resulting from all the phenotypes containing the silent gene is as low as 1 in 20 000 (deduced from table 2), it can be seen that, out of 100 subjects

sensitive to suxamethonium as a result of a genetic abnormality, 92 can be determined and anticipated by the routine preoperative estimation of the ChE level together with the DN and FN. A plea, therefore, is made that once a case of suxamethonium apnoea is encountered in hospital practice, there should be an organised machinery for ensuring that all relatives are screened at a specialised centre which is capable of dealing with the difficulties of phenotyping and of carrying out family studies.

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Table 2 is reproduced by kind permission of Dr Mary Whittaker and the Editor of *Anaesthesia*.⁴

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