SUCCINYLCHOLINE SENSITIVITY IN A NOVA SCOTIA FAMILY

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SUCCINYLCHOLINE is commonly used in anaesthesia when a short period of muscle relaxation is required. Muscle relaxation lasting two to five minutes follows a single intravenous dose of 1 mg/kg body weight. An occasional patient exhibits a prolonged period of muscle relaxation associated with so-called "succinylcholine apnoea".

Succinylcholine produces a depolarizing type of neuromuscular block during which the muscle is refractory to nerve stimulation. It is not clear exactly how it depolarizes but the most widely accepted explanation is that succinylcholine acts directly on the post-junctional membrane in the same manner as acetylcholine. An alternative theory postulates that succinylcholine produces depolarization indirectly by acting as a competitive inhibitor of acetylcholinesterase. In this way it blocks the hydrolysis of acetylcholine, so that prolongation of normal depolarization results which ceases only when the succinylcholine is hydrolyzed by circulating cholinesterase. Whatever the mode of action, full muscle power is normally restored within two to five minutes. This brief duration of action is largely the result of the hydrolysis of the drug in the circulation by the enzyme cholinesterase, 90 per cent of the injected dose being destroyed within the first minute.¹ Any failure in activity of this enzyme results in an overwhelming concentration of succinylcholine at the end plate, thereby prolonging the period of depolarization. The activity of serum cholinesterase thus plays an important part in determining the amount of relaxant which can reach the receptors. In the majority of cases of prolonged apnoea following succinylcholine there is a delay in hydrolysis of the injected succinylcholine due to the presence of an inherited defect in the enzyme cholinesterase.

Serum cholinesterase is formed in the liver. The enzyme is genetically determined by two allelic genes, neither of which shows dominance;

95 per cent of the population carry the normal or usual form (Table I). Abnormal variants of serum cholinesterase do occur which have a low affinity for succinylcholine, about 100-fold lower than that of the usual serum cholinesterase.¹ These abnormal variants may have low serum cholinesterase activity, but it would be misleading to rely on this as a screening procedure. Some patients with the phenotypes $E_1^a E_1^a$, $E_1^a E_1^f$, and $E_1^f E_1^f$, who are always sensitive to succinylcholine, have been shown to have normal serum cholinesterase activity with the usual assay substrates. The variant enzymes show a qualitative difference in a reduced ability to hydrolyze succinylcholine.

To identify the variants of serum cholinesterase, tests are performed using substances which inhibit their activity to different degrees. At present, four cholinesterase genes are generally recognized and described as the usual (u), atypical (a), fluoride-resistant (f), and silent (s) genes. The latter shows complete lack of cholinesterase activity and is one of the rarest encountered (Table I). Inhibitor substances found suitable for phenotyping cholinesterase are the local anaesthetic dibucaine (nupercaine, cinchocaine), fluoride, chloride and succinylcholine (Anectine, Scoline). The percentage inhibition under standard conditions is expressed as the respective number - dibucaine number (D.N.), fluoride number (F.N.), chloride number (C.N.), and scoline number (S.N.), (Fig. 1).

This report presents a Nova Scotia family in whom some members of the family had "difficulty in breathing" after anaesthesia. Subsequent investigations revealed the presence of several phenotypes of the enzyme cholinesterase, including individuals who were homozygous for the atypical cholinesterase gene.

CASE REPORT

In March, 1976, G.F., an otherwise healthy 15-year-old male, had suffered bilateral spontaneous pneumothorax. The right side had healed spontaneously, but in spite of underwater seal on three occasions, a 10 to 20 per cent pneumothorax persisted on the left side. He was referred

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TABLE I
FREQUENCY OF OCCURRENCE OF THE CHOLINESTERASE PHENOTYPES

Phenotype	Genotype	Frequency
Usual homozygote	$E_1^u E_1^u$	95 in 100
	$E_1^u E_1^s$	1 in 190
Usual/fluoride-resistant heterozygote	$E_1^u E_1^f$	1 in 280
Usual/atypical heterozygote	$E_1^u E_1^a$	1 in 26
Fluoride-resistant homozygote	$E_1^f E_1^{f*}$	1 in 300,000
	$E_1^f E_1^s$	1 in 200,000
Atypical/fluoride-resistant heterozygote	$E_1^a E_1^{f*}$	1 in 29,000
Atypical homozygote	$E_1^a E_1^{a*}$	1 in 2,800
	$E_1^a E_1^s$	1 in 20,000
Silent homozygote	$E_1^s E_1^{s*}$	1 in 140,000

*Phenotypes invariably sensitive to succinylcholine. (From J. King, Ph.D., Thesis, University of Glasgow, 1974.)

to the hospital and scheduled for a left pleurectomy and possible wedge resection of lung.

The pre-operative history revealed that he had no previous operations but that, on his father's side, several members of the family had experienced difficulties in recovering from anaesthesia. His father's in-patient records were immediately available and showed that in September 1975, while undergoing a cystoscopic examination, he had received succinylcholine 60 mg intravenously and had failed to breathe adequately for the next two hours.

In view of this story, succinylcholine was avoided during anaesthesia on the following day and again four months later when G.F. underwent a wedge resection of the right lung. On each occasion anaesthesia was induced with thiopentone and maintained with nitrous oxide, oxygen, and a narcotic, using pancuronium as the sole muscle relaxant. Both anaesthetics and the patient's recovery from them were uneventful.

FAMILY HISTORY

Detailed operation and anaesthetic histories were obtained about several members of the family; other information was obtained from various hospital, operating, anaesthetic and recovery room records. The relationship of the various members of the family to the patient is illustrated in Figure 2.

Patient No. 2, *Paternal grandmother*. 1962, Hysterectomy. Thiopentone, $N_2O - O_2$, di-ethyl ether, halothane. Recovery: no known difficul-

ties. 1965, Cholecystectomy. Thiopentone, succinylcholine, $N_2O - O_2$, halothane. Records state "patient became shocked, probably due to anoxia caused by anesthetic drugs". "Patient recovered after a few days on levophed, solucortef, oxygen."

Patient No. 3, *Paternal distant cousin*: age 26 - D and C for miscarriage. Anaesthetic records not available. Recovery: "did not recover consciousness". Died after one week, said to be an anaesthetic cause.

Patient No. 6 *Paternal aunt*. 1968, Caesarian section. Anaesthetic records not available. Recovery: "couldn't breathe", "wouldn't wake-up". Patient now carries a succinylcholine sensitivity card. Caesarian section X2 under spinal anaesthesia. Recovery: normal.

Patient No. 7, *Father*. 1974, Herniorrhaphy. Thiopentone, succinylcholine for intubation, nitrous oxide-oxygen, halothane. Quote from recovery-room records, "shallow breathing", ambu resuscitation: "twitching of body and extremities X 10 minutes", "extubated 1 hr 10 mins after start of anaesthesia", patient states "difficulty in breathing". Sept. 1975, Cystoscopy and retrograde pyelography. Thiopentone, nitrous oxide-oxygen halothane. Succinylcholine 60 mg given during pyelography. Respirations did not return in the expected time. Tracheal intubation and mechanical ventilation started. Extubated two hours after dose of succinylcholine. Nov. 1975, Nephrolithotomy. Thiopentone, nitrous oxide-oxygen, pancuronium, fentanyl. Recovery: normal.

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FIGURE 1. Ranges of inhibition found in cholinesterase phenotyping.

On the maternal side of the family no known anaesthetic difficulties had arisen. G.F.'s younger brother had a tonsillectomy some years before without complications but it is not known whether he received succinylcholine.

In view of the history, it was decided to investigate as many members of the family as were available for their cholinesterase activity and for any abnormal variants of the enzyme.

METHODS AND MATERIALS

Cholinesterase activity was measured by the method of Kalow and Lindsay² using a 50 μ mol/l benzoylcholine substrate. The percentage inhibitions of the enzyme by 10 μ mol/l dibucaine, 50 μ mol/l fluoride, 500 mmol/l chloride and 1 mmol/l succinylcholine were measured at 25° C according to the analytical scheme of King³ and King

FIGURE 2. Family relations to patient G.F.

and Griffin.⁴ The ranges of inhibition demonstrated by the different phenotypes are shown in Figure 1. The normal range of serum cholinesterase activity under these conditions is 620-1,370 U/l at 25° C.

RESULTS

The cholinesterase activity, inhibitor numbers and phenotype of each member of the family who was studied are contained in Table II and Figure 3.

The inhibitor numbers obtained for each family member using dibucaine (D.N.), fluoride (F.N.), chloride (C.N.), and succinylcholine (S.N.) are percentage inhibitions of the enzyme activity by each of the inhibitors. Clearly there are no "normal" inhibitor numbers and the numbers obtained are applied to Figure 1 to enable a phenotype to be assigned. The most frequently occurring phenotype is $E_1^a E_1^a$ since it occurs in 90 per cent of the population (Table I), but this has been carefully referred to as the "usual"

rather than a "normal" phenotype. The significance of the various phenotypes is dealt with in the discussion.

DISCUSSION

This case again emphasizes the value of taking a careful, detailed history from every patient. Questioning a patient before operation for details of previous anaesthetic events he or his family have experienced can yield important information. In this case, G.F. had no previous operation and quite possibly would have been given succinylcholine to facilitate tracheal intubation had he not told of his father's complications in recovery from anaesthesia. His father has the phenotype $E_1^a E_1^a$ (homozygous for the atypical gene) which means that he is always sensitive to succinylcholine. It would appear from the operative history that G.F.'s paternal grandmother had received succinylcholine by continuous intravenous drip for her cholecystectomy in 1965. She is also homozygous for the atypical cholin-

TABLE II

Patient number	Cholinesterase activity	Inhibitor numbers				Phenotype
		DN	FN	CN	SN	
1	358	15	23	56	7	$E_1^a E_1^a$
2 Grandmother	418	19	23	57	2	$E_1^a E_1^a$
5	467	14	23	57	17	$E_1^a E_1^a$
7 Father	541	18	18	57	6	$E_1^a E_1^a$
8	700	75	53	40	88	$E_1^u E_1^f$
9	436	66	42	29	67	$E_1^u E_1^a$
10	574 (568)	76	48	36	87	$E_1^u E_1^f$
12	685	79	58	11	91	$E_1^u E_1^u$
13	436	64	50	22	68	$E_1^u E_1^a$
14	733	65	51	20	71	$E_1^u E_1^a$
15 G.F.	364*	67	52	23	73	$E_1^u E_1^a$
	812†	65	46	20		$E_1^u E_1^a$
16	891	65	43	20	71	$E_1^u E_1^a$

*Patient's original sample - repeated and gave similar results.

†Recent sample from patient - repeated and gave similar results.

FIGURE 3. Phenotypes of family members.

terase gene, so that it is not surprising that her respirations were inadequate for some hours post-operatively. This illustrates the necessity for at least timing the response to a test dose of succinylcholine before using the drug by continuous drip.

Since the paternal grandparents of G.F. are both homozygous for the atypical gene, it follows that all their children must have $E_1^a E_1^a$ phenotype. Details of previous operations carried out on individuals on this side of the family are available. In four of these operations succinylcholine was used as a muscle relaxant and in

each case a prolonged apnoeic response occurred. No difficulties were recorded in the operations where succinylcholine was not used. It was unfortunate that at the time of the father's cystoscopic examination no details were obtained of the respiratory difficulties he had encountered during recovery from his previous operation.

The phenotype $E_1^a E_1^a$ is relatively rare (Table I) and along with $E_1^a E_1^f$, $E_1^f E_1^f$, and $E_1^s E_1^s$ represents the four phenotypes which invariably exhibit prolonged apnoea if challenged with succinylcholine. Sensitivity cards should always be issued to individuals possessing any of these four

phenotypes so that unnecessary anaesthetic complications can be avoided. It is important to remember that 50 per cent of cases of succinylcholine apnoea cannot be predicted and do occur in individuals who are homozygotes and heterozygotes of the usual enzyme. The very limited value of population screening, the correct terminology for the enzymes which hydrolyze choline esters and the relationship between cholinesterase activity to the length of the apnoeic response, have been recently reviewed.⁵

Our patient G.F. was never challenged with succinylcholine and since his phenotyping showed him to be heterozygous for the usual and atypical genes ($E_1^u E_1^a$), the outcome of any challenge with succinylcholine cannot be predicted. On his mother's side of the family four individuals have had previous operations with no known anaesthetic difficulties. It is not known definitely whether succinylcholine was given in any of those anaesthetics, but it is likely that it was used and indicates the unpredictable nature of any response in the presence of the heterozygous phenotypes ($E_1^u E_1^f$, $E_1^u E_1^a$). It is also possible that one of his mother's brothers (Figure 2, number 11), whom we have not had the opportunity of phenotyping, could be heterozygous for the atypical and fluoride resistant genes ($E_1^a E_1^f$) and therefore sensitive to succinylcholine.

If succinylcholine apnoea does occur, the patient and his family should be phenotyped and sensitivity cards issued if appropriate. It is better to investigate this selected population in detail rather than becoming involved in a population screening program with at best a 50 per cent success rate. A good history and testing of the families of individuals who have known sensitivity reactions can help to reduce the problems faced by anaesthetists. When succinylcholine sensitivity is suspected, all that is required is a 5 to 10 ml specimen of clotted venous blood for cholinesterase phenotyping. Should this prove to be one of the abnormal variants, further members of the family can then be investigated. It is not a disaster should "succinylcholine apnoea" occur unexpectedly. Management requires artificial ventilation, manual or mechanical, until normal respirations return. It is important to stress that no other physiological insult is directly produced by succinylcholine sensitivity and provided that adequate ventilation is maintained, there will be no occurrence of hypoxic "twitching of the body and extremities" as was recorded in the recovery room following the father's herniorrhaphy.

While incidents such as these occur in only a

small proportion of patients, they are not so rare as to make it unlikely to be experienced by many anaesthetists. It has been stated elsewhere that the patients and their families should be reassured that there is no other known penalty they have to pay as a result of their genetic sensitivity to succinylcholine. Simply avoiding the use of this drug and substituting another muscle relaxant prevents complications. The effectiveness of this simple measure of prevention has been amply illustrated by the operation records on the paternal side of the patient's (G.F.) family.

SUMMARY

Succinylcholine apnoea is usually the result of a delay in hydrolysis of the injected muscle relaxant due to the presence of an inherited defect in the enzyme cholinesterase.

This report presents a Nova Scotia family in whom several members had "difficulty in breathing" following anaesthesia. Subsequent investigations revealed the presence of several phenotypes of the enzyme cholinesterase including individuals who were homozygous for the atypical cholinesterase genes.

The frequency of occurrence and significance of the various phenotypes are discussed, together with their management and recommendations for family screening.

RÉSUMÉ

L'apnée prolongée secondaire à l'administration de succinylcholine est en général le résultat d'un retard d'hydrolyse de cet agent, dû à la présence d'une cholinestérase anormale. Cette anomalie, transmise génétiquement, est fonction de deux allèles non dominantes. Quarante-cinq pour cent de la population est porteuse de l'enzyme normale, alors que le cinq pour cent restant porte l'une ou l'autre des variantes anormales. Ces cholinestérases anormales qui ont une basse affinité pour la succinylcholine, peuvent être identifiées au moyen de substances inhibant leur activité à divers degrés. On connaît actuellement quatre variantes de la cholinestérase, soit la forme normale, l'atypique, la forme résistante aux fluorures et la forme silencieuse.

Les auteurs présentent le cas d'une famille de la Nouvelle Écosse dont plusieurs membres ont présenté des "problèmes de respiration" à la suite d'anesthésies. Une investigation des membres de cette famille a permis de reconnaître plusieurs porteurs de cholinestérases anormales.

Les auteurs discutent de la fréquence et de la signification des différentes formes anormales, ainsi que de la conduite anesthésique pour ces malades. Ils font aussi des remarques sur l'investigation des milieux familiaux suspects.

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