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Succinylcholine Neuromuscular Blockade in Subjects Homozygous for Atypical Plasma Cholinesterase

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Type, duration, and treatment of neuromuscular blockade following 1 mg/kg succinylcholine were studied on 16 occasions in 12 patients homozygous for atypical plasma cholinesterase during halothane–nitrous oxide–oxygen anesthesia using train-of-four (TOF) nerve stimulation. They were divided into four groups. In two cases the spontaneous recovery of the succinylcholine block was followed. In five cases the block was treated by intravenous injection of human cholinesterase (Cholase®, 90–270 mg) 30 min after succinylcholine. In five cases Cholase® (90–270 mg) was injected 90 min after succinylcholine. In the remaining four cases cholinesterase inhibitors were given either alone (one case) or in combination with Cholase® (three cases) 90 min after succinylcholine.

It was found that spontaneous resolution of the neuromuscular block had four phases: phase A (30–50 min)—complete neuromuscular block; phase B (20–25 min)—relatively rapid increase in both twitch height and TOF ratio; phase C (20–30 min)—a plateau phase; phase D (90–120 min)—a slow increase in TOF and, in the final part of this phase, an increase in twitch height as well. There was a pronounced fade of the TOF response in all patients in phases B, C, and D. Cholase® 30 min after succinylcholine improved neuromuscular transmission impressively within 5–10 min. After 90 min Cholase® had a much less pronounced effect. However, at this time the block could be completely reversed by a combination of Cholase® and a cholinesterase inhibitor.

The different results at 30 and 90 min presumably result from a change of the character of the block from a depolarizing to a desensitizing one (phase II block). Accordingly, rational treatment of such a block should include human cholinesterase for the depolarizing part of the block and a cholinesterase inhibitor for the desensitizing part of the block. (Key words: Antagonists, neuromuscular relaxants: edrophonium; neostigmine. Enzymes: atypical cholinesterase. Neuromuscular relaxants: succinylcholine. Neuromuscular transmission: stimulator, nerve; phase II block; tachyphylaxis.)

THE DURATION AND TYPE of succinylcholine neuromuscular blockade in subjects with genotypically normal plasma cholinesterase and in subjects heterozygous for abnormal plasma cholinesterase have been evaluated recently.[1,2] Similar studies in abnormal homozygotes have not been reported. The four allelic genes at locus E_1 controlling the synthesis of variants of plasma cholinesterase: E_1^u (usual), E_1^a (atypical), E_1^f (fluoride resistant), and E_1^s (silent) can give rise to three genotypes with homozygous occurrence of abnormal enzymes: E_1^s E_1^s, E_1^f E_1^f, and E_1^a E_1^a. Since the atypical gene (E_1^a) is by far the most common of the three abnormal genes, genotype E_1^a E_1^a is most important from a clinical point of view (1 in about 2,800 individuals have genotype E_1^a E_1^a).

The purpose of the present prospective controlled study was to evaluate type, duration, and treatment of the prolonged paralysis seen in patients homozygous for the atypical enzyme (E_1^a E_1^a) following an otherwise normal intubation dose of succinylcholine (1 mg/kg).

Materials and Methods

Twelve informed and consenting patients (ASA class I) anesthetized for elective surgery a total of 16 times were studied. The study plan was approved by the Ethical Committee at the hospital.

Eight patients had been referred to the Danish Cholinesterase Research Unit (DCRU)[3] because of prior experiences of prolonged apnea after succinylcholine. Four patients were members of families with known hereditary defects in plasma cholinesterase. There were eight females and four males. The average age was 37.7 yr (range: 20–71 yr) and the average body weight was 63.6 kg (range: 50–99 kg).

Diazepam, 0.15–0.20 mg/kg, was given orally 60 min before induction of anesthesia. Anesthesia was induced with 3.0–5.0 mg/kg thiopental and maintained with nitrous oxide 50 per cent and halothane 0.75–1.50 per cent inspired concentration. Ventilation was controlled manually. Following induction of anesthesia, neuromuscular function was monitored using train-of-four (TOF) nerve stimulation.[4] When the recorded response of the thumb to supramaximal stimulation of the ulnar nerve was stable (after 8–12 min), the height of the first twitch of the train was taken as the standard control (control twitch height). After at least 15 min at a stable halothane concentration 1 mg/kg succinylcholine was administered intravenously as a bolus and the patients were observed for muscle fasciculations. The patients were then divided into four groups. In Group I (Patients 1 and 2) spontaneous recovery following the administration of succinylcholine was followed, for 180 and 210 min, respectively. In Group II (Patients 3, 4, 5, 6, and 7) the neuromuscular block was treated by intravenous injection of highly purified human cholinesterase (Cholase®, 90–270 mg) 30 min after the administration of succinylcholine.† In Group III [Patients 2 (two anesthesias), 6 (two anesthesias), and 8 (one anesthesia)] the

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† The content of one ampoule of Cholase® (45 mg dried protein) corresponds to the amount of plasma cholinesterase in approximately 500 ml of human plasma.

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TABLE 1. Biochemical Characteristics of the Patients Homozygous for the Atypical Enzyme ($E_1^a E_1^a$). Means ± 2 SD and Ranges are Given. For Comparison Normal Range for Genotypically Normal Subjects ($E_1^u E_1^u$) are also Given[3]

Genotype	Number of Patients	Preoperative Cholinesterase Activity U/l	Dibucaine Number	Fluoride Number	Chloride Number	Scoline Number	Urea Number
$E_1^a E_1^a$	12	363 ± 211* (140–525)	22 ± 5 (18–26)	24 ± 9 (16–32)	52 ± 8 (46–58)	12 ± 9 (4–19)	97 ± 8 (87–100)
$E_1^u E_1^u$	453	677–1560*	78–86	55–65	1–12	89–95	41–52

* Indicate a significant difference.

neuromuscular function was allowed to recover partially for 90 min. At this time Cholase® (90–270 mg) was given intravenously. In Group IV (Patients 9, 10, 11, and 12) the neuromuscular function was also allowed to recover partially for 90 min. Cholinesterase inhibitors (edrophonium + neostigmine) were then given either alone (Patient 9), or in a combination with Cholase® (Patients 10, 11, and 12). Anesthesias in the same patient were at an interval of at least one year.

Blood samples for measuring plasma cholinesterase activity were drawn before anesthesia and again 10 min and 40 min after the administration of Cholase®. The activity was measured according to the procedure of Kalow and Lindsay,[5] and genetic variations of the enzyme were identified by the following methods: Dibucaine number,[6] fluoride number,[7] chloride number,[8] scoline number,[9] and urea number.[10]

The statistical analyses were performed using Mann Whitney rank sum test and Spearman test. Significance was assigned at a level of 0.01 or less.

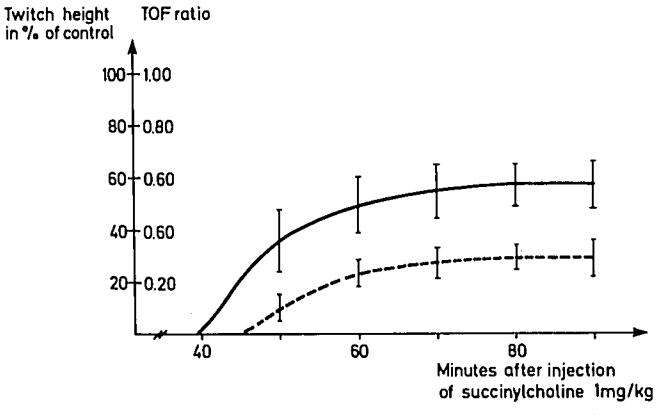

FIG. 1. Spontaneous recovery of thumb twitch (per cent of control) and train-of-four ratio following intravenous administration of 1 mg/kg succinylcholine in eight patients anesthetized a total of 11 times. (One patient was anesthetized twice and one patient three times; Groups I, III, and IV). See text for further explanation. Means ± SEM are given. (——) indicates twitch height, and (- - -) indicates TOF ratio.

Results

The biochemical cholinesterase characteristics of the 12 patients are summarized in table 1 and compared to that of normal subjects. In addition to abnormal characteristics, cholinesterase activity was reduced in the homozygotes.

Ten of 12 patients showed typical fasciculations in several muscle groups following succinylcholine. Onset time from injection of succinylcholine to disappearance of response to nerve stimulation (41.5 ± 8.0 s; mean ± SD) was not significantly different from onset time in normal patients[1] (40.3 ± 15.7 s). When the response to nerve stimulation reappeared all patients showed a marked "fade" of the TOF response already indicating a desensitizing block (phase II block).

In the patients allowed to recover spontaneously for 90 min (Groups I, III, and IV) a similar characteristic pattern of changes were seen in twitch height and TOF ratio (fig. 1). After an initial period of no response to nerve stimulation (phase A, mean 39 min, range 30–50 min) twitch height and TOF ratio increased for the next 20–25 min (phase B). This period of increasing response to nerve stimulation was succeeded by a plateau period of stable unchanged response (phase C, 20–30 min). In the two patients not treated after 90 min (Group I) TOF ratio started to increase again about 80 min after the injection of succinylcholine and the TOF ratio then increased slowly over the next 90–100 min (phase D; fig. 2). The twitch height, however, did not increase further for a period of about 60 min, and even decreased slightly for a period of about 40 min. The total times necessary for recovery of the TOF ratio to 0.7[11] were 137 and 152 min.

As expected[12] no relationship was found among these homozygote patients between preoperative plasma cholinesterase activity and the response to succinylcholine (time to first evoked response and to 20 per cent recovery of twitch height).

In Group II (Cholase® injected 30 min after succinylcholine) the first evoked twitch response appeared within 7 min of the injection in all five patients (table

2). During the following 10 min the twitch height increased rapidly with a mean increase in twitch height of 8.3 per cent of control per min (fig. 3 and table 2). Mean time to 90 per cent twitch recovery was 16 min (range: 4–28 min). Mean time to TOF ratio of 0.7 was 22.6 min (range: 5–33 min).

In Group III (Cholase® injected 90 min after succinylcholine) mean twitch height in per cent of control and mean TOF ratio were 40 per cent (range: 20–64 per cent) and 0.24 (range: 0.02–0.35), respectively, at the time of injection of Cholase® (table 2). In contrast to what was seen in Group II, injection of Cholase® did not have a pronounced effect on either the twitch or the TOF ratio. Recovery rates of twitch height in the first 10 min after the injection of Cholase® (mean 1.5 per cent of control per min, fig. 3 and table 2) were significantly lower than the corresponding recovery rates in Group II. No correlation was found between dose of Cholase® and recovery rates in Groups II and III.

In Group IV one patient was given only cholinesterase inhibitors beginning 90 min after succinylcholine (fig. 4). The initial injection of 10 mg edrophonium (preceded by 0.5 mg atropine) caused a pronounced but short-lived increase in both twitch height and TOF ratio. Administration of 2.0 mg neostigmine 10 min later was followed by a slow but steady increase in both parameters. Further neostigmine injection (1 mg) seemed to slow down the recovery. Following the last injection of neostigmine (0.5 mg; total dose 3.5 mg) both twitch height and TOF ratio decreased, and time to TOF 0.7 was 230 min. Another patient (not illustrated) was given 1.5 mg neostigmine (preceded by 0.5 mg atropine) intravenously 90 min after the injection of succinylcholine, followed 10 min later by a further 1.5 mg. As with the first patient, the twitch height and the TOF ratio increased initially, followed later by a decrease in both parameters. Cholase®, 125 mg, injected intravenously 40 min after the last admin-

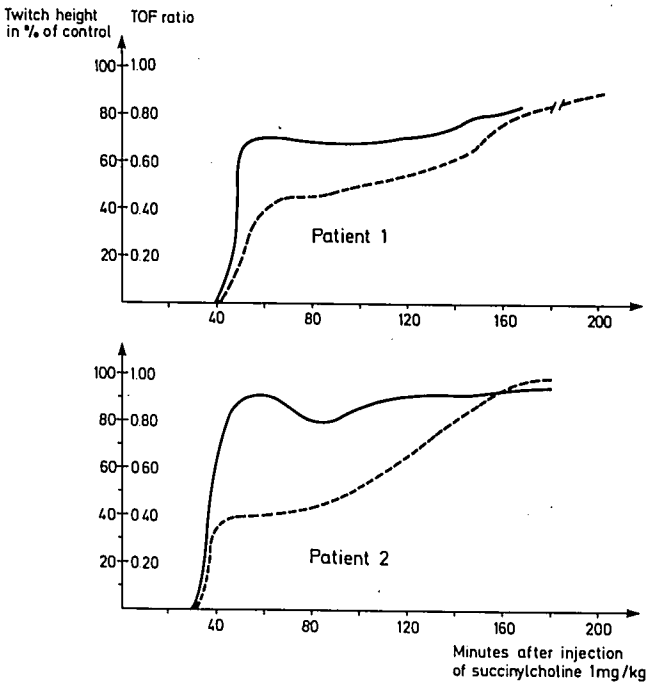

FIG. 2. Spontaneous recovery of thumb twitch and train-of-four ratio following intravenous administration of 1 mg/kg succinylcholine in two patients homozygous for the atypical enzyme (Group I). (——) indicates twitch height, and (- - -) indicates TOF ratio.

TABLE 2. Effect of Intravenous Injection of Cholase® 30 Min (Group II) and 90 Min (Group III), Respectively, after Intravenous Administration of 1 mg/kg Succinylcholine. Normal Range for Cholinesterase Activity (E_T^u E_T^u): 677–1560 U/l[3]

Group	Patient Number	Dose of Cholase®		Cholinesterase Activity (U/l)			Twitch Height in Per Cent of Control					Train-of-Four Ratio				
				Preoperatively	Min after Cholase®		Before Cholase®	Min after Cholase®				Before Cholase®	Min after Cholase®			
		Total	mg/kg		10	40		10	20	30	40		10	20	30	40
II	3	90	1.4	324	635	626	0	74	89	93	96	0.00	0.42	0.66	0.76	0.86
	4	180	2.5	520	1,190	1,090	0	70	80	100	105	0.00	0.35	0.55	0.82	0.90
	5	225	3.7	339	—	—	0	85	87	95	100	0.00	0.50	0.60	0.74	0.85
	6	270	2.7	587	1,310	1,262	0	85	100	105	108	0.00	0.45	0.62	0.75	0.85
	7	270	4.5	398	1,810	1,732	0	100	100	100	100	0.00	0.86	0.90	0.92	0.96
	MEAN	180	3.0	434	1,236	1,178	0	83	91	99	102	0.00	0.52	0.67	0.80	0.88
III	6	90	1.0	464	780	762	20	22	40	65	90	0.02	0.06	0.20	0.35	0.55
	8	90	1.8	282	819	800	64	73	81	92	100	0.35	0.47	0.62	0.83	0.96
	2	180	3.6	462	1,450	1,336	30	55	85	100	100	0.26	0.40	0.65	0.86	0.97
	6	270	3.0	458	1,324	1,253	55	70	91	108	111	0.26	0.34	0.56	0.71	0.90
	2	270	5.4	575	1,905	—	32	55	90	100	100	0.31	0.50	0.75	0.90	0.96
	MEAN	180	3.0	448	1,256	1,038	40	55	77	93	100	0.24	0.35	0.56	0.73	0.87

istration of neostigmine restored control twitch height and TOF ratio in 25 min. The last two patients in Group IV (only one illustrated) were given 90 mg Cholase® followed in 10 min by 10 mg edrophonium, and, another 10 min later, by 2.0 mg neostigmine (fig. 4). Following the injection of Cholase®, twitch height as well as TOF ratio increased slowly (cf. Group III). The subsequent injection of edrophonium and neostigmine, however, caused a marked and lasting improvement in neuromuscular transmission.

No side effects were seen in any patient following the injection of Cholase®.

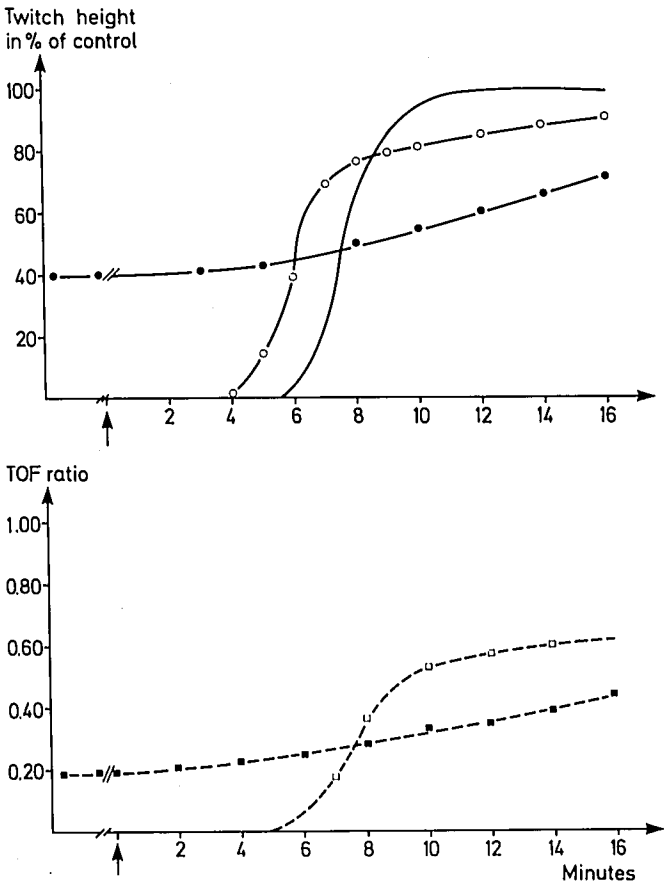

FIG. 3. Comparison of the initial recovery of neuromuscular transmission following intravenous administration of Cholase® 30 min and 90 min, respectively, after injection of 1 mg/kg succinylcholine. Arrows indicate injection of Cholase®. For graphic clarity only mean values are given (compare table 2). (O —— O) = mean twitch height in patients given Cholase® 30 min after the injection of succinylcholine (Group II, 5 patients). (● —— ●) = mean twitch height in patients given Cholase® 90 min after the injection of succinylcholine (Group III, 5 patients). (□ - - - □) = mean train-of-four ratio in Group II. (■ - - - ■) = mean train-of-four ratio in Group III. For comparison twitch recovery following the same dose of succinylcholine in 41 patients with normal cholinesterase activity and genotype (E_1^u E_1^u) is also shown (——).[1] Note the initial significantly increased recovery rate (increase in twitch height and TOF ratio per min) following the injection of Cholase® in Group II compared to Group III. See text for further discussion.

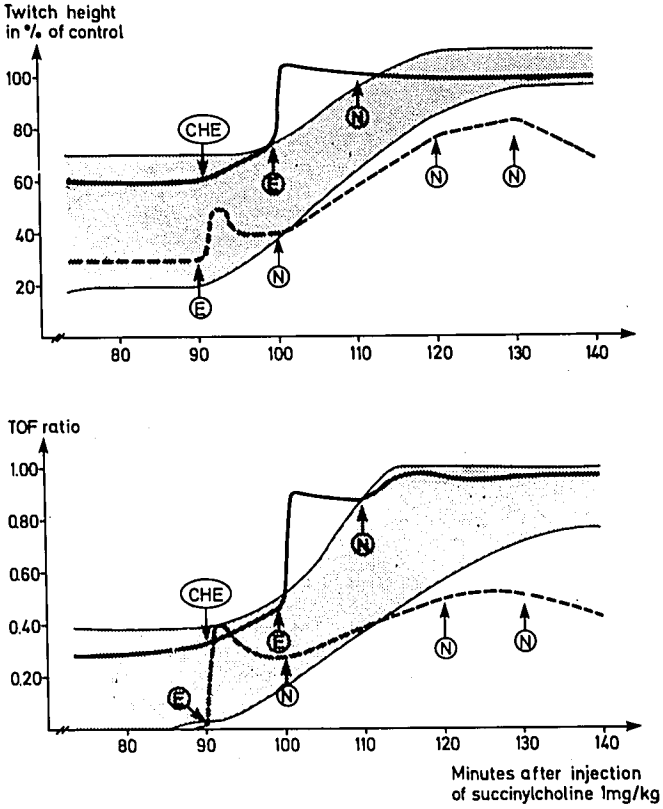

FIG. 4. Recovery of twitch height and train-of-four ratio in two patients homozygous for the atypical enzyme (Group IV). One patient (- - -) was given cholinesterase inhibitors only: 10 mg edrophonium (E) 90 min after succinylcholine and 2.0, 1.0, and 0.5 mg neostigmine, respectively, (N) 10, 30, and 40 min later. The other (——) was given 90 mg human cholinesterase (Che) intravenously 90 min after the administration of 1 mg/kg succinylcholine, followed in 10 and 20 min, respectively, by 10 mg edrophonium (E) and 2 mg neostigmine (N). Ranges of recovery of twitch height and train-of-four ratio in patients only given human cholinesterase (Group III) are shown for comparison (shaded areas). Note the fast recovery following the combination of human cholinesterase and acetylcholinesterase inhibitors. Note also the late depression of twitch height and train-of-four following treatment with acetylcholinesterase inhibitors only.

Discussion

Baraka[13] suggested that the appearance of muscle fasciculations following intravenous administration of succinylcholine excludes homozygous occurrence of atypical plasma cholinesterase (E_1^a E_1^a). However, 10 of 12 patients showed typical fasciculations following the injection of succinylcholine. These findings indicate that the appearance of fasciculations does not exclude the presence of genotype E_1^a E_1^a.

The times selected for the treatment of the block (30 and 90 min after injection of succinylcholine) were chosen for several reasons. Previous case reports of prolonged apnea after succinylcholine[14–16] in patients with genotype E_1^a E_1^a indicate that the patients have a desensitizing block 45–120 min after administration of succinylcholine. Whether the block is desensitizing from the start, or

whether an initial depolarizing block gradually changes to a desensitizing block is unknown. Brennan[17] was the first to report that succinylcholine in normal patients initially produces a depolarizing block which later, with increasing doses of succinylcholine, becomes a desensitizing block. Lee *et al.*[18] have recently shown, in normal patients anesthetized with enflurane, that this change in the character of the block occurs on the average 36 min after the start of a continuous infusion of succinylcholine (at the same time that tachyphylaxis develops). If the situation in the normal patient can be extrapolated to the situation in patients with genotype E_1^a E_1^a, administration of human cholinesterase 30 and 90 min after the administration of succinylcholine, respectively, should produce different effects. Thirty min after succinylcholine, a rapid resolution of the block should occur, paralleling the hydrolysis of succinylcholine in plasma. In contrast, 90 min after succinylcholine, when the block primarily should be desensitizing, the effect of human cholinesterase should be slow in onset (if there is any effect at all) since, at this time, block reversal is not only dependent on the concentration of free succinylcholine in the extracellular space, but possibly on the strength of the bond between succinylcholine and the end-plate receptors as well.[19,20] The effect of the administration of a cholinesterase inhibitor, such as neostigmine, must also depend on whether the neuromuscular block is depolarizing, desensitizing, or mixed. Accordingly, a pure desensitizing block should be reversible by neostigmine alone, whereas reversal of a block that is both depolarizing and desensitizing should possibly necessitate administration of both neostigmine and human cholinesterase.

The characteristic spontaneous four-phased course of the block can hardly be explained by changes in succinylcholine concentration in plasma. The atypical enzyme does not hydrolyze succinylcholine *in vivo*.[12] It is therefore improbable that the phase of rapid reversal (phase B) is due to enzymatic hydrolysis of succinylcholine. The rapid recovery may be due to the development of tachyphylaxis, analogous to what Gissen *et al.*[21] and Lee *et al.*,[18] among others, found in normal patients who have been given succinylcholine for prolonged periods of time. Since there was already fade of the TOF response in all patients when the first reaction to nerve stimulation could be elicited (30–50 min after succinylcholine), it is not possible to determine whether the development of tachyphylaxis and phase II are related, as held by Lee *et al,*[18] among others, or whether the development of tachyphylaxis is independent of the development of phase II block, as held by Ramsey *et al*[22] (among others). The speed of reversal during the last phase (phase D) is presumably dependent on the speed with which succinylcholine is removed from the blood and from the end-plate (by redistribution, urinary excretion, and alkaline hydrolysis).

Only two of the previously published case histories[14-16,23-26] seem to contradict the results presented here. Thus, Vickers[23] and Lear and co-workers[25] found that the neuromuscular block 90 and 240 min, respectively, after the injection of succinylcholine apparently still was depolarizing. In contrast, Bush,[14] Miller and Stevens,[16] Savarese *et al*,[15] Baraka,[26] and Telfer *et al*,[24] all found the neuromuscular block 45 to 120 min after administration of succinylcholine to be desensitizing (phase II).

It has never been documented through continuous monitoring of neuromuscular transmission that patients with genotype E_1^a E_1^a initially develop a depolarizing block after an intubation dose of succinylcholine (1 mg/kg). The results of this investigation (the short onset time, the lack of TOF fade during the onset of block, and the occurrence of fasciculations in 10 of 12 patients) and Baraka's[26] demonstration that the block after small doses of succinylcholine (0.1 mg/kg) seems to be depolarizing initially, speak for this being the case.

Injection of Cholase® 30 min after succinylcholine produced a pronounced increase in both twitch height and TOF ratio within 8–10 min in all five patients. In Patient 7, a twitch height of 100 per cent and a TOF ratio of 0.7 were reached after approximately 5 min. In the remaining four patients, the initial vigorous increase in twitch height and TOF was followed, however, by a slower rise (in TOF ratio in particular) and sufficient reversal of the block (TOF ratio ≥ 0.7) was first achieved after approximately 25 min. The rate of increase in twitch height after administration of Cholase® is similar to the spontaneous increase in twitch height seen after the same dose of succinylcholine given to genotypically normal patients.[1] However, after a little more than 2 min, the rate for the atypical patients decreases. The most obvious explanation for this is that the cholinesterase completely abolishes the depolarizing part of the neuromuscular block while the desensitizing part is only partly abolished. The situation is different when Cholase® is injected 90 min after the administration of succinylcholine (Group III). At this time, the desensitizing part of the block dominates so that the initial effect of the administered Cholase® is only modest. That the curves for twitch height and TOF ratios are parallel for the two groups of patients (Groups II and III) *after* the initial phase is over indicates that the flat part of the curves represents spontaneous resolution of the residual desensitizing block. Thus, anticholinesterases administered after the injection of Cholase® completely reversed the block in a few minutes, but not when given alone.

Only a few reports have been published describing the effects of human cholinesterase administration in cases of prolonged apnea from succinylcholine in patients homozygous for the atypical enzyme,[27-29] and evidently only two, in which the effect was evaluated using a nerve stimulator.[27,28] The findings of Goedde *et al*[27] in five

patients of rapid reversal of the block when Cholase® was injected a short time after the administration of succinylcholine are in complete agreement with the results of this study. Scholler and co-workers[29] found that the average recovery time (time to adequate spontaneous respiration) was 10 min (range 8–18 min), when Cholase® was injected after a mean time of 109 min (range 60–180 min). This is in contrast to the findings of this study of a slow recovery of neuromuscular function when Cholase® was injected 90 min after succinylcholine. However, none of the patients of Scholler and co-workers seem to have been monitored by a nerve stimulator. It is therefore possible that the block had not been reversed completely at the time when respiration was clinically judged to be sufficient.

Prolonged apnea after succinylcholine in patients with genetic anomalies of plasma cholinesterase has often been treated with cholinesterase inhibitors alone with mixed results.[14-16,23,24,26,30] The results seem to fall into three patterns: 1) sufficient reversal of the neuromuscular block[14-16,24]; 2) potentiation of the block[26]; or 3) initial short-lived, partial reversal of the block, followed by potentiation of the block.[14,15,30] The effect of neostigmine depends on whether there is free succinylcholine in plasma[21] (the block is potentiated if there is free succinylcholine in plasma) and to what extent the neuromuscular block is depolarizing or desensitizing. Furthermore, the dose of neostigmine is of importance; patients who received no more than 0.03 mg/kg neostigmine 1–2 hours after succinylcholine improved lastingly.[14-16] Doses in excess of this may slow down the recovery.

The results of this study indicate that theoretically, the rational approach to the neuromuscular block produced by 1 mg/kg succinylcholine in patients with genotype E_1^a E_1^a is to treat the depolarizing and the desensitizing parts of the block separately: for example, injection of 90–135 mg Cholase® will, within a few minutes, completely abolish the depolarizing part of the block and partly abolish the desensitizing part. Administration of, for example, neostigmine afterwards will then abolish the residual desensitizing part of the block.

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References

1. Viby-Mogensen J: Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with genotypically normal enzyme. ANESTHESIOLOGY 53:517–520, 1980
2. Viby-Mogensen J: Succinylcholine neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. ANESTHESIOLOGY (in press) 1981
3. Viby-Mogensen J, Hanel HK: A Danish cholinesterase research unit. Acta Anaesth Scand 21:405–412, 1977
4. Ali HH, Utting JE, Gray TC: Quantitative assessment of residual antidepolarizing block (Part I). Br J Anaesth 43:473–476, 1971
5. Kalow W, Lindsay HA: A comparison of optical and manometric methods for the assay of human serum cholinesterase. Can J Biochem 33: 568–574, 1955
6. Kalow W, Genest K: A method for the detection of atypical forms of human serum cholinesterase. Determination of dibucaine numbers. Can J Biochem 35:339–346, 1957
7. Harris H, Whittaker M: Differential inhibition of human serum cholinesterase with fluoride. Recognition of new phenotypes. Nature 191:496–498, 1961
8. Whittaker M: The pseudocholinesterase variants. Differentiation by means of sodium chloride. Acta Genet (Basel) 18:556–562, 1968
9. King J, Griffin D: Differentiation of serum cholinesterase variants by succinylcholine inhibition. Br J Anaesth 45:450–454, 1973
10. Hanel HK, Viby-Morgensen J: The inhibition of serum cholinesterase by urea. Mechanism of action and application in the typing of abnormal genes. Br J Anaesth 49:1251–1257, 1977
11. Brand JB, Cullen DJ, Wilson NE, et al: Spontaneous recovery from nondepolarizing neuromuscular blockade: Correlation between clinical and evoked responses. Anesth Analg (Cleve) 56:55–58, 1977
12. Kalow W: The distribution, destruction and elimination of muscle relaxants. ANESTHESIOLOGY 20:505–518, 1959
13. Baraka A: Absence of suxamethonium fasciculations in patients with atypical plasma cholinesterase. Br J Anaesth 47:419, 1975
14. Bush GH: Prolonged apnoea due to suxamethonium. Br J Anaesth 33:454–462, 1961
15. Savarese JJ, Ali HH, Murphy JD, et al: Train-of-four nerve stimulation in the management of prolonged neuromuscular blockade following succinylcholine. ANESTHESIOLOGY 42:106–111, 1975
16. Miller RD, Stevens WC: Antagonism of succinylcholine paralysis in a patient with atypical pseudocholinesterase. ANESTHESIOLOGY 36:511–513, 1972
17. Brennan HJ: Dual action of suxamethonium chloride. Br J Anaesth 28:159–168, 1956
18. Lee C, Barnes A, Katz RL: Magnitude, dose-requirement and mode of development of tachyphylaxis to suxamethonium in man. Br J Anaesth 50:189–194, 1978
19. Paton WDM: Mode of action of neuromuscular blocking agents. Br J Anaesth 28:470–480, 1956
20. Feldman SA: Muscle relaxants. Second edition. Philadelphia, London, Toronto, W. B. Saunders Company, 1979, pp 63–66
21. Gissen AJ, Katz RL, Karis JH et al: Neuromuscular block in man during prolonged arterial infusion with succinylcholine. ANESTHESIOLOGY 27:242–249, 1966
22. Ramsey FM, Lebowitz PW, Savarese JJ, et al: Clinical characteristics of longterm succinylcholine neuromuscular blockade during balanced anesthesia. Anesth Analg (Cleve) 59:110–116, 1980
23. Vickers MDA: The mismanagement of suxamethonium apnoea. Br J Anaesth 35:260–268, 1963
24. Telfer ABM, MacDonald DJF, Dinwoodie AJ: Familial sensitivity to suxamethonium due to atypical pseudocholinesterase. Br Med J 2:153–156, 1964
25. Lear E, Jadwat C, Bough L, et al: Atypical pseudocholinesterase: A clinical report. Anesth Analg (Cleve) 55:243–246, 1976
26. Baraka A: Suxamethonium-neostigmine interaction in patients with normal or atypical cholinesterase. Br J Anaesth 49:479–484, 1977
27. Goedde HW, Altland K, Scholler KL: Pharmakogenetische Reaktion auf Succinylcholin: Therapie der verlängerten Apnoe. Med Klin 62:1631–1635, 1967
28. Stovner J, Stadskliev K: Suxamethonium apnoea terminated with commercial serum cholinesterase. Acta Anaesth Scand 20:211–215, 1976
29. Scholler KL, Goedde HW, Benkmann H: The use of serum cholinesterase in succinylcholine apnoea. Can Anaesth Soc J 24:396–400, 1977
30. Hunter AR: Suxamethonium apnoea. A study of eighteen cases. Anaesthesia 21:325–336, 1966