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Succinylcholine Neuromuscular Blockade in Subjects Heterozygous for Abnormal Plasma Cholinesterase

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The relationship between plasma cholinesterase genotype and duration and type of succinylcholine neuromuscular blockade was studied in 43 anesthetized patients heterozygous for abnormal plasma cholinesterase using train-of-four nerve stimulation. Twenty-eight patients were heterozygous for the usual and the atypical gene ($E_1^uE_1^a$), eight were heterozygous for the usual and the silent gene ($E_1^uE_1^s$), three were heterozygous for the usual and the fluoride-resistant gene ($E_1^uE_1^f$), three were heterozygous for the fluoride-resistant and the atypical gene ($E_1^fE_1^a$), and one was heterozygous for the fluoride-resistant and the silent gene ($E_1^fE_1^s$).

Mean time to 90 per cent recovery of twitch height in patients with genotypes $E_1^uE_1^a$, $E_1^uE_1^s$, and $E_1^uE_1^f$ (14.6, 12.4, and 12.0 min, respectively) was significantly prolonged compared to patients with normal cholinesterase genotype (9.3 min). No significant difference was found between the three groups of patients with one abnormal gene ($E_1^uE_1^a$, $E_1^uE_1^s$, and $E_1^uE_1^f$). In 13 (46 per cent) of the 28 patients with genotype $E_1^uE_1^a$ the twitch height did not return to control for more than 15 min after the administration of succinylcholine and in three patients (10.7 per cent) for more than 20 min after succinylcholine.

The four patients with abnormal genes on both chromosomes ($E_1^fE_1^a$ and $E_1^fE_1^s$) all showed significantly prolonged paralysis following the administration of succinylcholine (mean time to 90 per cent twitch recovery was 30 min).

Patients heterozygous for the usual and one of the abnormal genes ($E_1^uE_1^a$, $E_1^uE_1^s$, and $E_1^uE_1^f$) had typically depolarizing blocks following the administration of succinylcholine, 1 mg/kg. Patients with abnormal genes on both chromosomes ($E_1^fE_1^a$ and $E_1^fE_1^s$), however, all showed desensitization type of neuromuscular blockade (phase II block). (Key words: Enzymes: abnormal cholinesterase. Neuromuscular relaxants: succinylcholine. Neuromuscular transmission: stimulator, nerve; phase II block.)

FOUR AUTOSOMAL ALLELIC GENES at locus E_1 control the synthesis of variants of the plasma cholinesterase enzyme: E_1^u (usual), E_1^a (atypical), E_1^f (fluoride-resistant), and E_1^s ("silent", not producing activity of cholinesterase). Combination of these genes can give any one of ten genotypes at locus E_1.

We have recently evaluated the correlation between plasma cholinesterase activity and duration of paralysis following succinylcholine in genotypically normal patients ($E_1^uE_1^u$).[1] However, the knowledge of the relationship between the different abnormal genotypes and response to succinylcholine is limited.[2] Therefore, we sought to quantify the relationship between duration and type of succinylcholine neuromuscular blockade and plasma cholinesterase genotype in patients heterozygous for abnormal plasma cholinesterase.

Materials and Methods

The study included 43 otherwise healthy, adult patients admitted for elective surgery. Twenty-eight patients were heterozygous for the usual and the atypical gene ($E_1^uE_1^a$), eight were heterozygous for the usual and the silent gene ($E_1^uE_1^s$), three were heterozygous for the usual and the fluoride resistant gene ($E_1^uE_1^f$), three were heterozygous for the fluoride resistant and the atypical gene ($E_1^fE_1^a$), and one was heterozygous for the fluoride resistant and the silent gene ($E_1^fE_1^s$).[3]

Five patients had been referred to the Danish Cholinesterase Research Unit (DCRU)[4] because of prolonged apnea after succinylcholine. Twenty patients were members of families with known hereditary defects in plasma cholinesterase. These patients had previously received a warning card against succinylcholine and consequently, the DCRU was contacted before the actual anesthesia. Eighteen patients were found by preoperative screening for abnormal plasma cholinesterase in patients admitted for elective surgery to our hospital. No patient had disease or received any drug that might alter neuromuscular function or depress cholinesterase activity. There were 25 females and 18 males. The average age was 47.7 years (range: 14–76).

Forty-one genotypically normal patients ($E_1^uE_1^u$) with normal enzyme activity served as a control group.[1]

The study was approved by the Herlev Hospital Human Study Committee, and informed consent was obtained from each patient.

Plasma cholinesterase activity (Che) 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 num-

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TABLE 1. Biochemical Characteristics of the Different Serum Cholinesterase Variants. Mean ± 2 SD and Ranges are given. For Comparison Normal Values (2.5 and 97.5 Percentiles) for Genotypically Normal Subjects (E_1^u E_1^u) are also Given[4]

Genotype	Number of Patients	Cholinesterase Activity (U/l)	Dibucaine Number	Fluoride Number	Chloride Number	Scoline Number	Urea Number
E_1^u E_1^a	28	762 ± 376 (285–1008)	64.7 ± 9.3 (51–70)	46.6 ± 7.8 (38–55)	23.4 ± 10.9 (13–34)	67.6 ± 16.2 (51–78)	61.3 ± 11.6 (55–71)
E_1^u E_1^s	8	515 ± 153 (412–620)	83.0 ± 2.6 (82–85)	60.3 ± 3.9 (57–62)	12.7 ± 4.7 (10–16)	90.2 ± 4.6 (86–93)	46.3 ± 5.2 (43–50)
E_1^u E_1^f	3	784 (579–900)	76.7 (74–80)	47.3 (47–48)	20.0 (14–30)	89.0 (87–91)	65.3 (64–67)
E_1^f E_1^a	3	553 (475–661)	50.7 (49–52)	28.3 (25–33)	34.0 (31–36)	57.0 (56–59)	92.7 (91–94)
E_1^f E_1^s	1	351	63	26	25	81	91
E_1^u E_1^u	453	677–1560	78–86	55–65	1–12	89–95	41–52

ber,[9] and urea number.[10] Family studies were also conducted when necessary for determining a correct genotype.

Diazepam, 0.15–0.20 mg/kg, was given orally 90 min before induction of anesthesia. Anesthesia was induced with thiopental, 3–5 mg/kg, and maintained with nitrous-oxide 50 per cent and halothane 0.75–1.50 per cent inspired concentration as indicated by a Fluotec® vaporizer. Ventilation was controlled, the aim being to keep the patients normoventilated. (Blood gases were monitored in a few patients.)

The ulnar nerve was stimulated at the wrist through cutaneous or percutaneous electrodes connected to a nerve stimulator. The adduction force of the resultant thumb twitch was measured by a displacement transducer [Statham UC 3 (gold cell)] and recorded on a polygraph. A series of four supramaximal single stimuli (rectangular pulses of 0.2-ms duration) was applied to the nerve at 2 Hz for 2 s every twelfth second (train-of-four).[11] When the response to the train-of-four nerve stimulation was stable (usually after 8–12 min), the height of the first twitch of the train was taken as the standard control (control twitch height). When the halothane concentration required for stable anesthesia had been given for at least 15 min succinylcholine, 1 mg/kg, was given intravenously, the patients were observed for fasciculations, and the duration of apnea (time to recurrence of spontaneous respiration) was recorded. Neuromuscular transmission monitoring was continued after succinylcholine administration at least until the height of the first twitch of the train had reached control twitch height. The times taken to first evoked response and to 25, 75, 90, and 100 per cent of the control twitch height were also recorded. The control twitch height was not reached in two

TABLE 2. Duration of Apnea and Time to Different Levels of Recovery of Twitch Height (First Twitch in the Train-of-Four Response) Following Succinylcholine, 1 mg/kg, Intravenously in 43 Patients with Heterozygous Occurrence of Abnormal Serum Cholinesterase and in 41 Patients with Normal Cholinestrase Genotype and Activity.[1] Mean ± 2 SD and Ranges are Given

Genotype	Number of Patients	Duration of Apnea (min)	First Evoked Response (min)	25 Per Cent Twitch Height (min)	75 Per Cent Twitch Height (min)	90 Per Cent Twitch Height (min)
E_1^u E_1^a	28	9.5 ± 4.8 (5.0–16.0)	9.9 ± 4.7 (4.5–15.0)	11.8 ± 5.0 (6.0–17.0)	13.7 ± 6.2 (7.5–21.0)	14.6 ± 6.9 (8.0–22.0)
E_1^u E_1^s	8	8.7 ± 5.8 (4.0–12.0)	7.8 ± 5.3 (4.0–11.5)	9.2 ± 5.7 (5.5–14.0)	10.8 ± 6.7 (7.0–16.0)	12.4 ± 7.9 (7.5–18.0)
E_1^u E_1^f	3	7.3 (7.0–8.0)	8.0 (6.5–9.0)	9.7 (9.0–10.0)	11.8 (11.0–12.5)	12.0 (11.0–13.0)
E_1^f E_1^a	3	24.0 (23.0–26.0)	23.5 (22.5–25.0)	25.3 (25.0–26.0)	28.3 (28.0–28.5)	29.5 (29.0–30.0)
E_1^f E_1^s	1	27.0	25.0	28.0	29.5	30.0
E_1^u E_1^u	41	5.8 ± 2.6 (4.0–9.0)	5.6 ± 2.1 (4.0–8.0)	7.0 ± 2.7 (4.5–10.0)	8.7 ± 3.1 (6.0–12.0)	9.3 ± 3.3 (6.0–13.0)

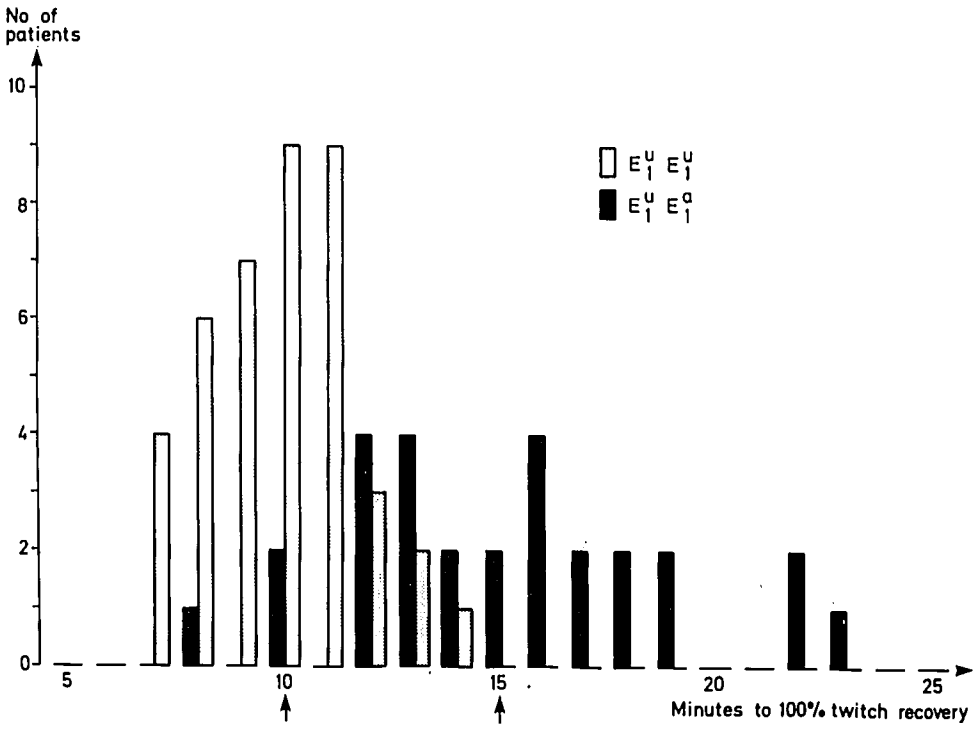

FIG. 1. Time to 100 per cent recovery of twitch height in 41 normal patients ($E_1^uE_1^u$) and in 28 patients heterozygous for the usual and the atypical enzyme ($E_1^uE_1^a$). Arrows indicate medians in the two groups of patients.

patients and the reference height was taken to be the height where the first twitches of the train-of-four records were stable after succinylcholine.

The statistical techniques used were Student's *t* tests and analyses of variance as well as a regression model developed by Lene Theil Skovgaard, Statistical Research Unit, Danish Medical and Social Science Research Councils.[1] This model describes a linear relation between the inverse plasma cholinesterase activity and duration of apnea and time to 100 per cent recovery of twitch height in subjects with normal cholinesterase genotype.

Results

Table 1 shows biochemical characteristics of the 43 patients. Overlapping in all five inhibitor numbers (but not in cholinesterase activity) was only seen in subjects with genotypes $E_1^uE_1^u$ and $E_1^uE_1^s$. Therefore, the presence of genotype $E_1^uE_1^s$ was always confirmed by family studies.

Twenty-one patients (75 per cent) with genotype $E_1^uE_1^a$, six patients (75 per cent) with genotype $E_1^uE_1^s$, two patients with genotype $E_1^uE_1^f$, and two patients with genotype $E_1^fE_1^a$ showed typical fasciculations in several muscle groups following the injection of succinylcholine.

The train-of-four ratios were indicative of a depolarizing type of neuromuscular block in all patients heterozygous for the usual and one of the abnormal genes ($E_1^uE_1^a$, $E_1^uE_1^s$, and $E_1^uE_1^f$). Patients with abnormal genes on both chromosomes ($E_1^fE_1^a$ and $E_1^fE_1^s$), however, showed fade in the response to train-of-four stimulation indicating a "desensitization" or phase II block.

Apnea periods and time to different levels of recovery of twitch height following injection of succinylcholine are shown in table 2. By one-way analyses of variance it was established for each of the five responses (duration of apnea, first evoked response, and 25 per cent, 75 per cent, and 90 per cent recovery of twitch height) that: 1) the responses from all six genotype groups could not be assumed equal (all $P < 0.0005$); 2) within the group defined by heterozygotes with one usual gene ($E_1^uE_1^a$, $E_1^uE_1^s$, $E_1^uE_1^f$) there was no significant differences (all $P > 0.1$); 3) the same was true (all $P > 0.1$) within the group ($E_1^fE_1^a$, $E_1^fE_1^s$) of heterozygotes without the usual gene (though this is only based on four patients); and 4) comparison of the group of 41 normal patients with normal cholinesterase activity ($E_1^uE_1^u$) with the group of heterozygotes with one usual gene showed significant differences (all $P < 0.005$).

The two larger groups ($E_1^uE_1^u$ and $E_1^uE_1^a$) are compared graphically in figure 1.

Whether the differences between genetic groups can be explained solely by differences in serum cholinesterase activity was studied via an application of the linear relationship between the inverse cholinesterase activity and duration of apnea and the time to

100 per cent recovery of twitch height developed earlier.[1] Regression analysis showed that the data for the $E_1^uE_1^a$ group easily accommodated a fit of this relationship (both $P > 0.1$). The duration of apnea as well as the time to 100 per cent recovery of twitch height for a given cholinesterase activity was significantly longer in the $E_1^uE_1^a$ group than in the $E_1^uE_1^u$ group, the difference being estimated as 3.1 min and 4.7 min, respectively with standard errors of 0.4 and 0.5 min, respectively (both $P < 0.0001$).

Discussion

Baraka[12] suggested that the appearance of muscle fasciculations following the administration of succinylcholine excludes the presence of atypical plasma cholinesterase (homozygotes). However, I found typical fasciculations in around 75 per cent of the patients investigated. Thus, the appearance of fasciculations does not exclude heterozygous occurrence of abnormal cholinesterase.

Since approximately 2.5 per cent of patients are heterozygous for the usual and atypical enzyme ($E_1^uE_1^a$),[13] knowledge of this genotype's reaction to succinylcholine is most important. Breakdown of succinylcholine in such patients is commonly presumed to occur normally.[14,15] Case histories, however, indicate that certain patients with this genotype can be unusually sensitive to succinylcholine.[2,14,16,17] Lehman and Liddell[15] and Das[18] have estimated, respectively, that approximately one in every 480 and one in every 400 patients with the genotype $E_1^uE_1^a$ are unusually sensitive to succinylcholine. We have previously suggested a somewhat higher frequency based on genotype determinations in patients referred to the Danish Cholinesterase Research Unit because of prolonged apnea.[2]

Such estimations of sensitivity, however, are for the most part based on investigations where the reaction to succinylcholine is clinically evaluated without the use of a nerve stimulator. The uncertainty of such clinical investigations is illustrated by one of our own patients who developed apnea lasting 60 min after 1 mg/kg succinylcholine,[2] while during a subsequent anesthesia, normal neuromuscular transmission, judged by a nerve stimulator, returned 22 min after the same dose of succinylcholine. Thus, the prolonged apnea during the first anesthesia was presumably a result of other factors.

The present investigation showed that in 13 patients (46 per cent) with genotype $E_1^uE_1^a$, the twitch height returned to control twitch height more than 15 min after the administration of succinylcholine, and in 10.7 per cent of the patients more than 20 min after succinylcholine (fig. 1). The clinical implication of these increases in neuromuscular blockade is normally of minor consequence. However, if the cholinesterase activity is depressed, *e.g.*, because of a concomitant disease or pregnancy, a clinically significant prolonged paralysis may result.

Because of the relatively limited number of patients with genotype $E_1^uE_1^s$ and $E_1^uE_1^f$, it is difficult to make a general statement about how patients with these genotypes will react to succinylcholine. A clinically significant prolonged action of succinylcholine normally is not to be expected in these patients following succinylcholine, 1 mg/kg. It is worth noting, however, that three patients with genotype $E_1^uE_1^s$, first returned to control twitch heights after 16, 17, and 20 min, respectively.

Patients with heterozygous occurrence of two abnormal genes ($E_1^fE_1^a$ and $E_1^fE_1^s$) reacted quite differently to succinylcholine than did patients with only one abnormal cholinesterase gene ($E_1^uE_1^a$, $E_1^uE_1^s$, and $E_1^uE_1^f$). Not only were duration of apnea and the time to the various stages of twitch recovery significantly prolonged in these patients, but the type of block was different as well. While there was no fade in the train-of-four ratio in patients with heterozygous occurrence of one normal and one abnormal gene, the four patients with genotypes $E_1^fE_1^a$ and $E_1^fE_1^s$ all showed fade in the response to train-of-four stimulation. In genotypically normal subjects ($E_1^uE_1^u$), succinylcholine initially produces a depolarizing block which later, with increasing doses of succinylcholine, becomes desensitizing. Subjects with genotypes $E_1^fE_1^a$ or $E_1^fE_1^s$ do not have the normal cholinesterase enzyme. The hydrolysis of succinylcholine is therefore slower than in normal subjects and 1 mg/kg succinylcholine will represent a relative overdose. This may explain the occurrence of phase II block in these patients. It is uncertain whether the phase II block was of any clinical importance in the relation to a single 1 mg/kg injection of succinylcholine. Thus, recovery time (*e.g.*, the time from the first evoked response to 90 per cent twitch height; table 2) was of the same order of magnitude as for the other genotypes, and the train-of-four ratio at 100 per cent twitch recovery was ≥ 60 per cent in all four patients.[19] Respiration was judged sufficient at this time in the four patients. On the other hand, the presence of fade in the response to train-of-four stimulation can critically alter the reaction to repeated doses of succinylcholine. Accordingly, 1 mg/kg succinylcholine was repeated 45 min after the first injection in the patient with the genotype $E_1^fE_1^s$.[3] Just as after the first injection, twitch height returned to 100 per cent in 31 min, but at this time the train-of-four ratio was 0 and there were only weak insufficient

respiratory movements. The train-of-four ratio just reached 60 per cent after an additional 34 min had passed.

Train-of-four stimulation was chosen for this investigation because through this mode of stimulation changes in type and degree of block can be followed continuously. A normal response to train-of-four stimulation, however, does not mean normal function of the neuromuscular end-plate. More than 70 per cent of the end-plate receptors can be completely nonfunctioning without affecting the response to train-of-four stimulation.[20] (Application of tetanic stimulation, 100–200 Hz, will result in normal response only at lesser degrees of receptor occlusion, but tetanic stimulation may disturb subsequent measurements.) Thus, a normal response to train-of-four stimulation a certain number of minutes after a single injection of succinylcholine does not prove that the neuromuscular end-plate is unaffected by succinylcholine. Therefore, it cannot be excluded that patients with genotypes $E_1^uE_1^a$, $E_1^uE_1^s$ and $E_1^uE_1^f$ might have developed fade in the response to train-of-four stimulation were the initial succinylcholine dose greater than 1 mg/kg or were the succinylcholine repeated (cf. the effect of a second dose of succinylcholine in the patient with genotype $E_1^fE_1^s$). Similarly, precurarization with a small dose of a nondepolarizing relaxant could modify the reaction to succinylcholine as well. The anesthetic used (halothane) also influences neuromuscular transmission[21,22] and it is possible that some of the fade seen in the train-of-four responses in patients with genotypes $E_1^fE_1^a$ and $E_1^fE_1^s$ was due to halothane. This does not change any of the qualitative or quantitative differences demonstrated between patients with genotypes $E_1^uE_1^a$, $E_1^uE_1^f$, and $E_1^uE_1^s$, on the one hand, and patients with genotypes $E_1^fE_1^a$ and $E_1^fE_1^s$, on the other hand, since all patients received halothane.

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