Correlation of Succinylcholine Duration of Action with Plasma Cholinesterase Activity in Subjects with the Genotypically Normal Enzyme

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In a recent analysis of 225 cases of prolonged apnea following succinylcholine administration reported to the Danish Cholinesterase Research Unit, we found that 14 patients (6.2 per cent) had low plasma cholinesterase activity (cholinesterase: E.C. 3.1.1.8, acetylcholine acylhydrolase) due to an acquired deficiency. The durations of apnea following administration of succinylcholine, 50–250 mg (mean ± SE: 102 ± 14.7 mg) in these 14 patients ranged from 15 to 240 min (mean ± SE: 82 ± 20.8 min). These figures are not consistent with the generally accepted point of view that even a marked deficiency in enzymatic activity causes only moderate prolongation of the period of apnea following succinylcholine.

Only one of these 14 patients was tested pre- and postoperatively with a nerve stimulator. In some cases, the prolonged apnea may have resulted from other factors, such as hyperventilation and/or residual narcotic effect. We, therefore, sought to quantify the relationship between duration of succinylcholine-induced neuromuscular blockade and cholinesterase activity in patients with genotypically normal plasma cholinesterase.

**Materials and Methods**

From November 1977 to December 1978, plasma cholinesterase activity and dibucaine number were determined for 826 patients admitted for elective surgical procedures to our hospital. Patients who had plasma cholinesterase activities less than 680 (normal range: 677–1560 U/l) or dibucaine numbers less than 80 (normal range: 78–86) were further investigated for abnormal cholinesterase genotypes by the following determinations: fluoride number, chloride number, scoline number, and urea number. When the heterozygous occurrence of silent and usual enzymes was suspected, family studies were also conducted. Patients who had abnormal genotypes were excluded. All genotypically normal patients with low (n = 23) or high (n = 6) plasma cholinesterase activity and 41 patients with normal cholinesterase, selected at random, were included in the study. Thus, the final number of patients studied was 70, 43 women and 27 men of average age 46.3 years (range: 15–86 years).

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Group I comprised 23 patients with low activities (mean ± SE: 512.2 ± 34.3 U/l, range: 154–675 U/l); the 41 patients in Group II had normal plasma cholinesterase activities (mean ± SE: 891.5 ± 29.2 U/l, range: 677–1430 U/l); and the six patients in Group III had high plasma cholinesterase activities (mean ± SE: 1795.0 ± 109.6 U/l, range: 1631–2334 U/l).

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 Flumotec® vaporizer. Ventilation was assisted or controlled as needed.

Following induction, 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-msec duration) was applied to the nerve at 2 Hz for 2 sec every twelfth sec (train-of-four\textsuperscript{10}). When the response to the train-of-four 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). Succinylcholine, 1 mg/kg, was given intravenously, and the duration of apnea (time to recurrence of spontaneous respiration) was recorded. Monitoring of neuromuscular transmission was continued after succinylcholine administration, at least until the height of the first twitch of the train had reached the control twitch height. The times taken to first evoked response and to 25, 75, 90, and 100 per cent of the control

| Table 1. Durations of Apnea and Times to Different Levels of Recovery of the Control Twitch Height (First Twitch in the Train-of-four Response) Following Administration of Succinylcholine, 1 mg/kg, iv, to 70 Patients with the Normal Plasma Cholinesterase Genotype (Means ± 2 SD and Ranges) |
|---------------------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                                                   | 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) |
| Group I: low enzymatic activity                   | 23                | 8.3 ± 6.5 (5.0–21.0)   | 8.1 ± 5.1 (4.5–15.5)   | 9.7 ± 5.3 (70.0–173.3) | 11.4 ± 6.0 (8.0–20.0) | 11.6 ± 5.0 (9.0–21.0) |
| Group II: normal enzymatic activity               | 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 (6.0–15.0)  |
| Group III: high enzymatic activity                | 6                 | 3.7 ± 2.5 (2.5–5.0)    | 3.7 ± 2.3 (2.5–5.0)    | 4.9 ± 2.8 (3.0–6.5)   | 6.4 ± 2.6 (4.5–7.5)   | 7.3 ± 3.3 (6.0–9.0)   |
twitch height were also recorded. Three patients did not reach the control twitch height, and the reference height was taken to be that height where the first twitches of the train-of-four records were stable after succinylcholine administration.

**RESULTS**

Periods of apnea and times to different levels of recovery of twitch height following the injection of succinylcholine are shown in table 1. The train-of-four ratios (the ratio of the height of the fourth to that of the first resultant twitch in the train) were indicative of a depolarizing type of neuromuscular blockade in all patients, and there was no relationship between plasma cholinesterase activity and train-of-four ratio either before or after succinylcholine administration.

Figures 1 and 2 show the relationships between plasma cholinesterase activities and durations of apnea and times to 100 per cent twitch recovery, respectively. Linear relationships were found between the inverse plasma cholinesterase activity and the duration of apnea and the time to 100 per cent recovery of twitch height.

**DISCUSSION**

The results of this study show that for patients with the genotypically normal enzyme the duration of succinylcholine action increases with decreasing plasma cholinesterase activity.

The majority of studies of possible correlation between plasma cholinesterase activity and duration of apnea following succinylcholine were made before the discovery of the different genotypes of plasma cholinesterase and/or were retrospective studies of only a few patients who experienced prolonged apnea. Some found good correlation between the esterase level and duration of apnea, while others found only partial correlation or no correlation at all.

Since the discovery of hereditary defects in plasma cholinesterase as a cause of low enzymatic activity, at least four more studies have been reported. Both Kalow and Gunn and Stoddart found correlations between the durations of apnea after succinylcholine and esterase levels (51 and 31 patients, respectively). However, the studies of Kalow and Gunn were published four years before the discovery of the fluoride-resistant gene, and Stoddart did not investigate his patients for hereditary defects in plasma cholinesterase. Hunter, who measured only the dibucaine numbers, found no correlation between esterase level and duration of apnea (41 patients). None of these investigators monitored neuromuscular function.

Blitt et al., using single-twitch nerve stimulation, were unable to demonstrate a correlation between esterase activity and duration of paralysis after succinylcholine administration in 50 patients. The discrepancy between this finding and our results may reflect that Blitt's patients showed only minor variations in enzymatic activities.

In summary, we found that it is possible to predict...
duration of apnea and time to 100 per cent twitch recovery following administration of succinylcholine, 1 mg/kg, iv, to patients with known (genotypically normal) plasma cholinesterase activity. Slightly prolonged paralysis may occur when esterase activity is between 400 and 500 U/L, but even esterase activity as low as 150–200 U/L causes only moderate prolongation of the duration of apnea and time to 100 per cent twitch recovery (maximal time to 100 per cent twitch recovery was 22 min). This suggests that the markedly prolonged apnea seen in some of the 14 patients described in previous reports was due to factors other than low plasma cholinesterase activity.

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