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# *Effects of Neostigmine and Pyridostigmine on Duration of Succinylcholine Action and Pseudocholinesterase Activity*

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**Effects of the anticholinesterase drugs on the duration of action of succinylcholine (SCh) and pseudocholinesterase activity were studied in 16 adult patients undergoing general anesthesia. Each patient received two doses of SCh, 1 mg/kg, intravenously: the first dose was given before and the second dose, 5 min after neostigmine, 5 mg, or pyridostigmine, 25 mg. Electromyographic determinations were used to measure the duration of SCh-induced block. Prolongation in the neostigmine group (n = 8) was compared with that in the pyridostigmine group (n = 8). Pseudocholinesterase activities were determined before, during, and at the point of full recovery of neuromuscular blockade by the second dose of SCh.**

**The effect of SCh, 1 mg/kg, was significantly prolonged from the control value, 11.1 ± 1.43 (mean ± SE), to 35 ± 3.24 min following neostigmine, and from 13.1 ± 1.45 to 23.9 ± 2.5 min after pyridostigmine. Pseudocholinesterase activities determined 5 min after administration of neostigmine and pyridostigmine were decreased to 21 and 20 per cent of control, respectively. Full recovery from the SCh-induced block was observed, while enzymatic activities remained suppressed to 47 and 39 per cent of control in the neostigmine and pyridostigmine groups, respectively. The neuromuscular blocking effect of SCh was significantly prolonged by both neostigmine and pyridostigmine, but more by neostigmine. It is concluded that the enzyme may not be the sole factor determining the effect of anticholinesterase drugs on the duration of action of SCh. (Key words: Antagonists, neuromuscular relaxants: neostigmine; pyridostigmine. Enzymes: pseudocholinesterase; cholinesterase. Neuromuscular relaxants: succinylcholine.)**

PROLONGATION AND POTENTIATION of the neuromuscular effect of succinylcholine (SCh) following administration of anticholinesterase drugs in man have been reported by a number of investigators.[1–5] The precise mechanism of prolongation remains unresolved. This investigation was designed to observe the extent of prolongation of SCh-induced block, pseudocholinesterase activity changes, and possible correlation of the two by measuring the serial changes of the enzymatic activities during the process of the recovery from neuromuscular blockade by SCh, which had been given shortly after the administration of an anticholinesterase drug.

## Methods

Sixteen adult patients scheduled for elective surgical procedures were informed of the nature and objectives of the study, and consent was obtained from each patient. The study protocol and consent forms were approved by the local committee for human protection.

The study group consisted of 13 male and three female patients of ASA Physical Status 1, ranging in age from 25 to 68 years (mean 49 years) and in weight from 65 to 90 kg (mean 75 kg). Patients who had histories of major organ diseases, or any abnormal laboratory finding, especially electrolyte, acid–base and fluid disturbances, were not included in the study. Those who were receiving long-term drug therapy of any kind or antibiotics were also excluded. Each subject was premedicated with a combination of appropriate doses of diazepam or pentobarbital, meperidine, and atropine given intramuscularly. A venous blood sample was drawn in the operating room before an intravenous infusion was started for a determination of control pseudocholinesterase activity and dibucaine number. Intubation of the trachea was carried out following administration of thiopental, 4 mg/kg, and SCh, 1 mg/kg, and anesthesia was maintained with nitrous oxide–oxygen supplemented with narcotic drugs (meperidine or fentanyl). Ventilation was controlled throughout the operation at a tidal volume of 10 ml/kg and a rate of 12 breaths/min. Esophageal or rectal temperature was monitored during the study period.

Following an induction dose of thiopental, but before administration of SCh, muscular responses to single (twitch) and multiple (tetanic) stimuli were monitored with an oscilloscope and recorded on electromyographic (EMG) paper using a TECA TE-4 EMG. The amplitudes of these responses were measured and they served as control. Single supramaximal (0.1-msec duration at 0.5–1.0-Hz frequencies) and multiple (50 Hz for 3–5 sec) stimuli were applied to the ulnar nerve at the elbow and electrical responses were obtained via two surface electrodes applied to the abductor digiti minimi. SCh, 1 mg/kg was then administered intravenously. Muscular responses to the single repeated stimuli were continuously monitored with an oscilloscope until these responses return to control

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(pre-SCh) level. EMG recording was again made at this point and the amplitude of electrical responses measured. Following this first dose of SCh, we measured 1) the time from the point of disappearance of muscular responses to the point of the first evidence of return of muscular responses (complete paralysis phase, $T_1$); 2) the time from the point of the first evidence of return of muscular responses to full recovery—this phase was coincided clinically with the return of twitch (twitch recovery phase, $T_2$); 3) the total duration of action ($T_1 + T_2$). Five minutes after full recovery was confirmed, either neostigmine, 5 mg, or pyridostigmine, 25 mg, mixed with atropine, 2 mg, was administered intravenously as a bolus. These large doses were chosen in order to see how the maximum clinical reversal dose of neostigmine or pyridostigmine would affect the pseudocholinesterase activity and duration of SCh subsequently given.

Five minutes later, a second venous blood sample was drawn for pseudocholinesterase determination. This was immediately followed by a second dose of SCh, 1 mg/kg, given intravenously. EMG monitoring of the evoked muscular responses and measurement of the durations of each phase of recovery time ($T_1$, $T_2$, and $T_1 + T_2$) were performed in the same fashion as with the first dose of SCh. A third venous blood sample was taken at the point of onset of twitch return and a fourth venous blood sample was drawn at the time of full recovery. These samples were tested for pseudocholinesterase activity during the course of muscular recovery from the SCh given 5 min after the anticholinesterase administration.

In the first 14 of the 16 patients studied, pseudocholinesterase levels were also determined 5 min after the first dose of SCh in order to determine whether enzymatic activity changed following SCh administration. All enzymatic determinations were performed by Bio-Science Laboratories.‡

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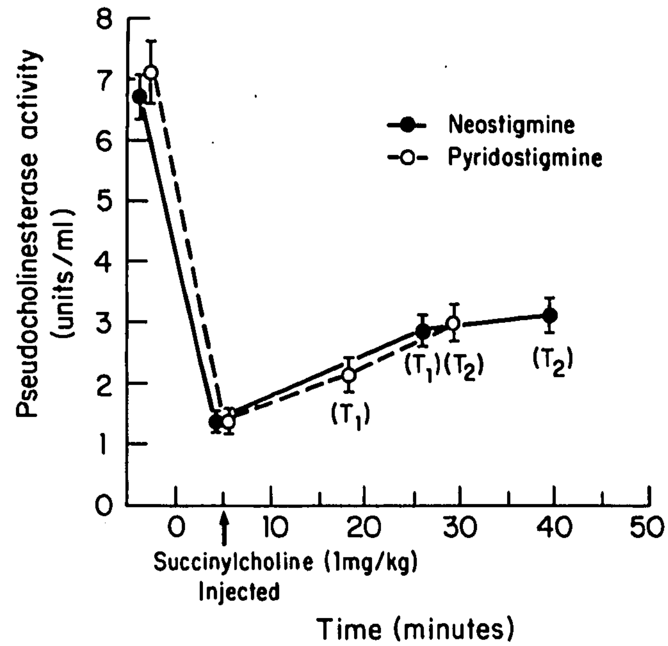


FIG. 1. Correlation between pseudocholinesterase activity and duration of neuromuscular blocking effect of SCh, 1 mg/kg, injected intravenously 5 min after administration of neostigmine, 5 mg, or pyridostigmine, 25 mg. $T_1$ represents the point of the first evidence of twitch return and $T_2$, full recovery.

The extents of prolongation of SCh effect and amounts of pseudocholinesterase suppression in the neostigmine (n = 8) and pyridostigmine (n = 8) groups were compared. The data were analyzed using Student's t test. $P < 0.05$ was considered significant.

## Results

Pseudocholinesterase activity was decreased from a mean of 6.65 to 1.41 units/ml (21 per cent of control) by neostigmine and from 7.15 to 1.4 units/ml (20 per cent of control) by pyridostigmine 5 min following the administration of each drug (table 1 and fig. 1). Enzymatic activities at the onset of twitch return were 2.77

TABLE 1. Pseudocholinesterase Activities* (Means ± SE)

| | Control | 5 Min after Anticholinesterase | At the Onset of Twitch Return | At the Time of Complete Recovery |
|---|---|---|---|---|
| Neostigmine group (N = 8) | | | | |
| Pseudocholinesterase (u/ml) | 6.7 ± 0.4 | 1.4 ± 0.1† | 2.8 ± 0.3† | 3.1 ± 0.3† |
| Pseudocholinesterase, per cent of control | | 21 | 42 | 47 |
| Pyridostigmine group (N = 8) | | | | |
| Pseudocholinesterase (u/ml) | 7.2 ± 0.5 | 1.4 ± 0.1† | 2.2 ± 0.2† | 2.8 ± 0.3† |
| Pseudocholinesterase, per cent of control | | 20 | 31 | 39 |

* Normal value: 3–8 units/ml.
† $P < 0.05$.

TABLE 2. Durations of Action (Means ± SE) of Succinylcholine, 1 mg/kg, iv, before and after Administration of Neostigmine or Pyridostigmine

| | Neostigmine Group (n = 8) | | Pyridostigmine Group (n = 8) | |
|---|---|---|---|---|
| | First Dose (Control) | Second Dose (After Anti-cholinesterase) | First Dose (Control) | Second Dose (After Anti-cholinesterase) |
| Minutes from complete paralysis to first evidence of twitch return: Complete inhibition time ($T_1$) | 6 ± 0.8 | 22.1 ± 1.6* | 6.5 ± 0.6 | 14.6 ± 1.7* |
| Minutes from first evidence of twitch return to full recovery: Twitch recovery time ($T_2$) | 5.1 ± 0.9 | 12.9 ± 2.0* | 7.5 ± 1.3 | 9.3 ± 1.2 (*N.S.*) |
| Total duration of action ($T_1$ and $T_2$) (min) | 11.1 ± 1.4 | 35 ± 3.2* | 13.1 ± 1.5 | 23.9 ± 2.5* |

* $P < 0.05$.

units/ml (42 per cent of control) for the neostigmine group and 2.2 units/ml (31 per cent of control) for the pyridostigmine group. Pseudocholinesterase activities were still less than 50 per cent of the control values at the time of full recovery of muscular activity.

The neuromuscular blocking effect of SCh, 1 mg/kg, was significantly prolonged from the control value by both neostigmine and pyridostigmine (table 2). However, the SCh effect was more prolonged following neostigmine, and this difference between the two was statistically significant.

Pseudocholinesterase activities determined 5 min after the first intravenously administered dose of SCh, 1 mg/kg, in 14 patients showed an average decrease of 15 per cent, which was not statistically significant.

## Discussion

Stoelting[6] recently emphasized the need to decrease the dose of SCh following the use of neostigmine or pyridostigmine, and a special caution was given concerning pyridostigmine because it produced the more profound inhibition of pseudocholinesterase. Our data, however, show that at equipotent doses (5:1 ratio)[7] the neostigmine group had a more than threefold prolongation of SCh effect compared with less than a twofold prolongation in the pyridostigmine group.

The magnitude and duration of the enzymatic depression in our study do not agree with those of Stoelting,[6] who observed a prompt return of enzymatic activity with neostigmine (no longer significantly decreased after 10 min), while the enzyme remained significantly decreased even after 120 min with pyridostigmine. Enzymatic changes in our study were similar in the two groups during the first 30 min, and more than 50 per cent depression persisted even 40 min after neostigmine (fig. 1). The larger doses of anticholinesterase drugs we used may explain in part the discrepancy between our results and those of Stoelting.

The correlation between decreased pseudocholinesterase activity and prolongation of SCh-induced block has been reported in the literature in cases of patients with normal enzymes (not atypical type).[8-10] These reports have indicated that enzymatic activities should be greatly decreased (less than 25 per cent of normal) before any significant prolongation of SCh effect is observed. In our study, full recovery from SCh-induced block was demonstrated while the pseudocholinesterase activity remained below 50 per cent of control in both groups, even though SCh, 1 mg/kg, was given at the time of a profound depression of enzymatic activity (20 per cent of control).

Regarding the two phases of SCh-induced block, Walts and Dillon demonstrated that the first complete inhibition phase was dose-related, and the second twitch recovery phase was not significantly different over a wide range of doses of SCh in patients with normal pseudocholinesterase activity.[11] Our data showed that the complete paralysis phase ($T_1$) was strikingly extended by both neostigmine (3.6-fold) and pyridostigmine (2.9-fold), indicating the higher concentration of SCh available in the blood and more drug reaching the end plate of the neuromuscular junction during the redistribution period, due to the decreased enzymatic hydrolysis of SCh in the blood. The twitch recovery phase ($T_2$) was slightly increased by neostigmine, but there was no significant change by pyridostigmine. The difference in the $T_1$ phases appeared to be largely responsible for the greater prolongation observed in the neostigmine group.

One of the possible mechanisms that may explain the difference between the durations of SCh-induced blocks in the two groups is that the acetylcholine accumulated at the neuromuscular junction could cause an additive effect on SCh-induced paralysis[2] and this effect might have caused a longer $T_1$ phase in the neostigmine group because of the faster onset of action of neostigmine as an antagonist of nondepolarizing drugs in comparison with pyridostigmine.[7]

Furthermore, a direct depolarizing action of neostigmine at the neuromuscular junction[12] might have contributed to the prolongation of SCh-induced block in both phase $T_1$ and phase $T_2$. This direct action is known to be absent with pyridostigmine.[13]

In conclusion, pyridostigmine produced less prolongation of SCh-induced block than neostigmine, although it was found to be a longer-acting drug as an antagonist for nondepolarizing muscle relaxants.[7] From the clinical standpoint, one must expect a moderate increase in the duration of action of SCh when it is used following neostigmine or pyridostigmine reversal, but an excessive prolongation of more than an hour would not be likely even with the maximum clinical concentration of either drug. Since we found differences in the enzymatic activities as well as in times to recovery from SCh-induced block between the neostigmine and pyridostigmine groups, we reasonably assume that pseudocholinesterase activity is not the single determinant for the prolonged response to SCh administered following neostigmine or pyridostigmine.

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## References

1. Thesleff S: An investigation of the muscle-relaxing action of succinyl-choline-iodide in man. Acta Physiol Scand 25:348–367, 1952
2. Gissen AJ, Katz RL, Karis JH, et al: Neuromuscular block in man during prolonged arterial infusion with succinylcholine. Anesthesiology 27:242–249, 1966
3. Bentz EW, Stoelting RK: Prolonged response to succinylcholine following pancuronium reversal with pyridostigmine. Anesthesiology 44:258–260, 1976
4. Foldes FF, Hillmer NR, Molloy RE, et al: Potentiation of the neuromuscular effect of succinylcholine by hexafluorenium. Anesthesiology 21:50–58, 1960
5. Scaf AHJ, Van Den Akker J, Westenberg HGM: The role of cholinesterase in the neuromuscular effects of succinylcholine, decamethonium and hexafluorenium. Arch Int Pharmacodyn Ther 208:177–192, 1974
6. Stoelting RK: Serum cholinesterase activity following pancuronium and antagonism with neostigmine or pyridostigmine. Anesthesiology 45:674–677, 1976
7. Miller RD, Van Nyhuis LS, Eger EI II, et al: Comparative times to peak effect and durations of action of neostigmine and pyridostigmine. Anesthesiology 41:27–33, 1974
8. Evans FT, Gray PWS, Lehmann H, et al: Sensitivity to succinylcholine in relation to serum cholinesterase. Lancet 1:1229–1230, 1952
9. Argent DE, Dinnick OP, Hobbiger F: Prolonged apnoea after suxamethonium in man. Br J Anaesth 27:24–30, 1955
10. Vickers MD: The cholinesterases and their significance to the anaesthetist using muscle relaxants. Br J Anaesth 35:528–534, 1963
11. Walts LF, Dillon JB: Clinical studies on succinylcholine chloride. Anesthesiology 28:372–376, 1967
12. Riker WF Jr, Wescoe WC: Studies on the inter-relationship of certain cholinergic compounds. J Pharmacol Exp Ther 100:454–464, 1950
13. Hobbiger F: The action of carbamic esters and tetraethylpyrophosphate on normal and curarized frog rectus muscle. Br J Pharmacol 5:37–48, 1950