Characteristics of the Neuromuscular Block With Succinylcholine and Decamethonium in Man

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Characteristics of the neuromuscular block produced by succinylcholine and by decamethonium were studied in 32 subjects anesthetized with halothane. Electromyograms (EMG) and tension of the adductor pollicis brevis muscle were recorded simultaneously. The neuromuscular block presented from the onset the typical characteristics of a phase II block: fade of EMG amplitude and fatigue of muscle tension during tetanization, as well as post-tetanic facilitation. Phase I neuromuscular block, characterized by constant tetanic responses of EMG and tension, and by absence of post-tetanic facilitation was never observed, even with smallest effective blocking doses of succinylcholine or decamethonium. Fade of EMG and fatigue of tension increased proportionately with block; the more profound the block, the more pronounced the fade and fatigue. Whereas fade and fatigue increased progressively as more drug was given, post-tetanic facilitation was related neither to dosage nor to duration of administration of the drug. Thus facilitation was of little value in defining state of neuromuscular block during prolonged administration. The neuromuscular block produced by succinylcholine and decamethonium had from its onset the electromechanical characteristics of a phase II block. Hence phase I and phase II block cannot be differentiated on the basis of muscle response to nerve stimulation.

Early observations led to the belief that decamethonium and succinylcholine produced a pure depolarization block in all mammals, including man. Later studies indicated that in some species these drugs exhibited a dual mode of action characterized by the production of an initial depolarization block (phase I) which gradually changed to a non-depolarization block (phase II). The shift from phase I to phase II neuromuscular block was subsequently demonstrated in man for both succinylcholine and decamethonium.

Churchill-Davidson et al. recorded the electromyogram (EMG) evoked by nerve stimulation and characterized the type of neuromuscular block according to the following criteria: (1) ability of the motor end plate to transmit impulses at tetanic rates; (2) presence or absence of post-tetanic facilitation; and, (3) effect of anticholinesterase drugs on the neuromuscular block. They found in man that phase I block changed to phase II only after the administration of 6 to 20 mg. of decamethonium or 500 to 1,500 mg. of succinylcholine. Applying the same criteria, but recording muscle tension instead of EMG, Katz et al. recently observed a phase shift in man with much smaller doses of succinylcholine (1–2 mg./kg. body weight). Crul and his co-workers demonstrated the shift in phase with even smaller doses of succinylcholine (0.6 mg./kg.). Phase II block described by these investigators was apparently always preceded by a phase I block, characterized by well-sustained tetanic response and/or absence of post-tetanic facilitation.

The original purpose of this investigation was to determine whether the difference in dosage of succinylcholine or decamethonium required to produce a shift in phase might be attributed to the different methods of studying the effect of neuromuscular blocking agents. To test this hypothesis we recorded EMG and muscle tension simultaneously.

The unexpected result of our study was that, from its onset, the neuromuscular block produced by succinylcholine or decametho-
nium was characterized by both fade of EMG and fatigue of muscle tension during tetany, and by post-tetanic facilitation. A phase I block, identified by well-sustained tetanic responses and absence of post-tetanic facilitation was never seen, even when small blocking doses of these agents were used. On the basis of our findings, a redefinition of the characteristics of neuromuscular block produced by succinylcholine and decamethonium may be in order.

**Methods**

Thirty-two patients aged 19 to 60 years (median 32 years), scheduled for surgical operations on the head, limbs or lower abdomen, were studied. The 18 female and 14 male subjects were free of neuromuscular disease. Informed consent for performance of the investigation was obtained the day before operation. Patients were medicated with pentobarbital (Nembutal) (100–150 mg.) and atropine or scopolamine (0.3–0.6 mg.). Before induction of anesthesia, two needle electrodes were inserted subcutaneously, 2 cm. apart, over the ulnar nerve at the wrist. One EMG disc electrode was placed over the belly of the adductor pollicis brevis muscle and one over the tendon of insertion. The thumb was slipped through a loop attached to a rigidly mounted tension transducer (Grass, model FT-10). Forearm, wrist and hand were then securely fixed to a padded board, leaving only the thumb free.

The nerve was supramaximally stimulated with transformer-isolated pulses of 0.25 msec. duration, delivered by a square-wave generator (Grass, model S-8). The stimulation sequence was programmed as follows: a single pulse (pre-tetanic test twitch), followed in 10 seconds by a 5-second-long tetanic burst, at a frequency of 40 Hz, which in turn was followed 2 seconds later by a single post-tetanic pulse. Muscle action potentials were amplified and displayed on one oscilloscope channel (Tektronix, model 565). Output of the tension transducer was carrier-amplified and displayed on the second channel. EMG and tension traces on the oscilloscopic screen were photographed on 35-mm. film moving at a speed of 10 mm./sec. Amplitude of EMG in millivolts and muscle tension in grams were measured on magnified film.

After a sleep dose of thiopental, anesthesia was induced with a nitrous oxide-oxygen-halothane mixture and carried to sufficient depth to permit endotracheal intubation without the use of a muscle relaxant. Inspired halothane concentration was then decreased to between 0.8 and 1.5 per cent according to surgical requirements, then held constant. Following equilibration with halothane for at least 45 minutes, control records of neuromuscular responses were obtained. From 2 to 5 mg. decamethonium (12 subjects) or 10 to 20 mg. succinylcholine (20 subjects) were then rapidly injected intravenously. Pulmonary ventilation was assisted or controlled as required.

The neuromuscular response to larger drug doses was subsequently studied in 30 of the 32 subjects. Succinylcholine, 0.1 to 0.2 per cent solution, was given to 17 subjects as a continuous intravenous infusion. The rate of administration was adjusted to maintain neuromuscular transmission (see below) between approximately 20 and 40 per cent of control value. Recordings were made after each 10 mg. increment, up to the first 100 mg., then after each 50 mg. increment of succinylcholine. Infusion was halted at intervals to observe recovery of neuromuscular function and resumed when transmission reached 80 to 90 per cent of control. Total doses of succinylcholine varied from 100 to 700 mg. (mean, 360 mg.): maximum time of administration was 3.5 hours.

Decamethonium was given intravenously intermittently in equal increments of 2.5 to 4.0 mg. (1 mg./20 kg. body weight) to 13 subjects. The initial dose reduced neuromuscular transmission to 5 to 15 per cent of control values. Subsequent doses were given when neuromuscular transmission had returned to 60 to 80 per cent of control values (every 20 to 45 minutes). Total doses of decamethonium varied between 5 and 16 mg. (mean, 8.6 mg.), given in 2 to 4 fractional doses. The effect was studied for 2 to 4.5 hours and recordings were made periodically at various levels of neuromuscular transmission.
Neuromuscular transmission was expressed as the ratio of experimental to control (pretetanic test) EMG in per cent. A ratio of 100 per cent implied normal transmission; zero indicated complete neuromuscular block. The time course of tetanic muscle tension was expressed as the ratio of lowest to highest tension—the tetanic tension ratio—within each tetanic train. A ratio of 100 per cent meant that muscle tension remained constant (i.e., was well-sustained) throughout the five-second period of tetany. The EMG response during tetanization was similarly expressed as the ratio of lowest to highest EMG amplitude—the tetanic EMG ratio—within each tetanic train.

Post-tetanic facilitation, the heightened response following tetanic contraction, was expressed in terms of the pre-tetanic test response. The ratio of the post-tetanic twitch amplitude to the corresponding pre-tetanic test amplitude, was called the post-tetanic tension ratio. The post-tetanic EMG ratio was similarly calculated. A ratio greater than 100 per cent indicated post-tetanic facilitation. Facilitation was however considered significant only when it exceeded 200 per cent.

Regression lines for tetanic and post-tetanic responses on percentage neuromuscular transmission, drug dose, and time were calculated by the method of least squares. The best-fitting regression equation relating the sets of observations was calculated with the aid of a digital computer (IBM 7094), programmed for multiple regression analysis. Regression coefficients as well as total and partial correlation coefficients were calculated, and analyzed for statistical significance. Data were plotted as scattergrams, onto which the calculated regression equation was projected.

Results

Control records obtained during halothane anesthesia, just before injection of muscle relaxant, showed well-sustained EMG and tension responses during the five-second tetanization periods (figs. 1 and 2, control). Some post-tetanic facilitation was consistently pres-
Decamethonium ≤ 4 mg

Fig. 3. Scattergram and calculated regression line of tetanic EMG ratio versus neuromuscular transmission. Data obtained from 12 subjects given 4 mg. decamethonium or less. Note that as neuromuscular transmission decreases, the tetanic EMG ratio also decreases.

ent before injection of muscle relaxant. Control post-tetanic EMG and tension ratios were always greater than 100 per cent though never more than 150 per cent (figs. 1 and 2, control). We, therefore, considered post-tetanic facilitation meaningful only when the ratio exceeded 200 per cent.

Upon injection of succinylcholine or decamethonium, block of neuromuscular transmission developed, as shown by a decrease in amplitude of the test twitch EMG and tension. Concomitantly the tetanic EMG and tension ratios fell, and post-tetanic facilitation of EMG and tension increased. As drug dosage was increased, the responses showed quantitative changes. The results are therefore presented separately for the small and large doses.

Small Doses. Small doses of succinylcholine, 20 mg. or less, and decamethonium, 4 mg. or less, produced a neuromuscular block of short duration and rapidly changing magnitude. At equivalent levels of depression of neuromuscular transmission the block exhibited similar characteristics in all subjects. The tetanic EMG and tension ratios were markedly reduced (figs. 1 and 2). This response, fade of EMG and fatigue of tension, was consistently seen, even with the smallest effective dose of succinylcholine (10 mg.) or decamethonium (2 mg.).

Scattergrams of the tetanic EMG and tension ratios plotted against the percentage of neuromuscular transmission for decamethonium are shown in figures 3 and 4. Statistical analysis of the regression revealed, for both succinylcholine and decamethonium, a significant \( P < 0.001 \) positive linear association between percentage of neuromuscular transmission and tetanic EMG and tension ratios. In other words, the more complete block, the more fade and fatigue.

Post-tetanic EMG and tension ratios were similarly plotted against percentage of neuromuscular transmission. Post-tetanic facilitation was significant (>200 per cent) only when neuromuscular transmission was less than approximately 20 per cent. Under these conditions, post-tetanic ratios as high as 550 per cent were observed for EMG and tension. In summary, fade of EMG, fatigue of tension, and post-tetanic facilitation were seen even with the smallest effective single doses of succinylcholine or decamethonium.

Succinylcholine—Large Doses. As additional drug was given, the tetanic tension

Decamethonium ≤ 4 mg

Fig. 4. Scattergram and calculated regression line of tetanic tension ratio versus neuromuscular transmission. Data obtained from 12 subjects given 4 mg. decamethonium or less. Note that as neuromuscular transmission decreases, the tetanic tension ratio also decreases.
FIG. 5. Electromyogram (upper tracings) and isometric tension (lower tracings) after administration of 0, 20, 100 and 250 mg succinylcholine. Note progressive fall in maximal tetanic tension and increasing fatigue with larger doses of succinylcholine; EMG changes parallel tension changes. Post-tetanic facilitation is seen in all records, including control. The tetanic tension ratio is 95, 38, 12 and 10 per cent and the post-tetanic ratio is 138, 226, 210 and 276 per cent at, respectively, 0, 20, 100 and 250 mg succinylcholine.

ratio, at a given level of neuromuscular transmission, became progressively lower. For example, at 50 per cent neuromuscular transmission, the mean tetanic tension ratio was 49 per cent after the first 20 mg of succinylcholine, 43 per cent after 100 mg., and 15 per cent after 500 mg. This progressive fall of tetanic tension ratio with increasing dosage is illustrated in figure 5. The level of neuromuscular transmission is approximately the same (20–30 per cent) in these records, but the tetanic tension ratio decreases (fatigue becomes more profound) as more succinylcholine is given.

Analysis of the multiple regression of tension ratio on dose of succinylcholine and on neuromuscular transmission (137 observations) yielded the equation: $Y = 15.1 + 0.70X_1 - 0.07X_2$, with Y the tetanic tension ratio in per cent, $X_1$ the neuromuscular transmission in per cent and $X_2$ the dose of succinylcholine in milligrams. The regression coefficients for transmission and dose differed significantly from zero ($P < 0.001$). The correlation between the tetanic tension ratio and either transmission ($r_{x1} = 0.708$) or dose ($r_{x2} = 0.357$) was significant ($P < 0.001$). The partial correlation $^8$ between tetanic tension ratio and transmission at fixed dose levels ($r_{x1, x2} = 0.739$) was also significant ($P < 0.001$). Thus, the tetanic tension ratio is linearly and directly related to neuromuscular transmission, and linearly but inversely related to dose of succinylcholine.

From the preceding equation it can be seen that, for a given dose of succinylcholine, the tetanic tension ratio is smaller if neuromuscular transmission is lower. In other words, the more profound the neuromuscular block, the more profound the fatigue. Furthermore, as already mentioned, for a given level of neuromuscular transmission the tetanic tension ratio falls progressively as more succinylcholine is given. The relationship between tetanic tension ratio and dose and neuromuscular transmission is shown in figure 6.

Data relating the post-tetanic tension ratio to neuromuscular transmission and dose of suc-

FIG. 6. Scattergram of tetanic tension ratio versus dose of succinylcholine, for neuromuscular transmission in the range of 25 to 75 per cent. Calculated regression lines at 75 per cent (upper line) and at 25 per cent neuromuscular transmission (lower line). Note progressive decline in the tetanic tension ratio with increasing dose.
cylcholine were treated similarly. The best-fitting equation (168 observations) was: \( Y = 219.1 - 0.91X_1 - 0.02X_2 \), with \( Y \) the post-tetanic tension ratio in per cent, \( X_1 \) the neuromuscular transmission in per cent and \( X_2 \) the dose of succinylcholine in milligrams. The regression coefficient of transmission \( (X_1) \) differed significantly from zero \((P < 0.001)\), but the coefficient of dose \((X_2)\) did not \((P > 0.1)\). The partial correlation coefficient between post-tetanic tension ratio and succinylcholine dose at fixed levels of transmission \((r_{yx1^2} = -0.51)\) confirmed the lack of association between post-tetanic tension ratio and dose.

To show more clearly the association between post-tetanic tension ratio and level of neuromuscular transmission the equation was recalculated to exclude dosage. The new equation became: \( Y = 216.4 - 0.90X \), with \( Y \) the post-tetanic tension ratio and \( X \) the percentage of neuromuscular transmission. The linear association between these two parameters was significant \((r = -0.490; P < 0.001)\). To summarize, post-tetanic facilitation is linearly and inversely related to neuromuscular transmission only, and bears no relation to dose of succinylcholine (fig. 7). The post-tetanic EMG ratio showed a parallel trend.

**Decamethonium—Large Doses.** Since decamethonium was given in fractional doses, with intervening partial recovery of transmission, the additional factor of time was also taken into consideration. Regression analysis (211 observations) yielded the equation: \( Y = 38.5 + 0.58X_1 - 6.42X_2 + 0.28X_3 \), where \( Y \) is tetanic tension ratio in per cent, \( X_1 \) is neuromuscular transmission in per cent, \( X_2 \) is dose of decamethonium in milligrams, and \( X_3 \) is time in minutes. All three regression coefficients differed significantly from zero \((P < 0.001)\). The partial correlation coefficients between tetanic tension ratio and transmission and dose and time, respectively, indicated a strong linear association, significant at the \( P < 0.001 \) level \((r_{yx2^3} = 0.865; r_{yx2^3} = -0.835 \text{ and } r_{yx2^3} = 0.797)\). Thus, for decamethonium also, the tetanic tension ratio is linearly and directly related to neuromuscular transmission and to time, and linearly and inversely related to dose. In other words, muscle fatigue becomes more intense when neuromuscular block is more profound or when more decamethonium is given; conversely, muscle fatigue decreases as neuromuscular transmission improves and as time progresses, provided no more drug is given. The progressive de-
crease in tetanic tension ratio with successive doses of decamethonium is apparent in figure 8.

Correlation analysis of the post-tetanic tension ratio included, in addition to dose and neuromuscular transmission, the variable of time. Solution for these four parameters (205 observations) yielded an equation which, on analysis, showed a significant linear association only between tetanic tension ratio and neuromuscular transmission. The partial correlation coefficients between post-tetanic tension ratio and dose of decamethonium and time (with the remaining two parameters fixed) were, respectively, $r_{x2.x1.x3} = 0.153$ and $r_{x2.x1.x4} = -0.172$; these were not significant ($P > 0.1$). The data therefore were recalculated to find the relation between post-tetanic tension ratio and transmission alone. The new equation became: $Y = 173.3 - 0.55X$, where $Y$ is the tetanic tension ratio and $X$ the neuromuscular transmission, both expressed in per cent. The correlation coefficient was $r = -0.396$; the linear association was therefore significant ($P < 0.001$). Thus, for decamethonium, also, the post-tetanic tension ratio is linearly and inversely related to percentage of neuromuscular transmission, and bears no relation to either dose of decamethonium or to time. In other words, post-tetanic facilitation becomes more apparent as the neuromuscular block is made more profound, independent of dose (fig. 9). The post-tetanic EMG ratio showed a corresponding trend.

**Discussion**

We have shown that the neuromuscular block produced by succinylcholine and by decamethonium is characterized, from its very onset, by fade of tetanic EMG, fatigue of tetanic tension and development of post-tetanic facilitation. These are the commonly accepted characteristics of a phase II block in man. At no time did we observe a phase I block (well-sustained tetany and lack of post-tetanic facilitation) either with small or large drug doses.

Our results differ from those previously obtained in man, possibly on the basis of experimental methods or anesthetic used. We studied the adductor pollicis brevis muscle, which probably approaches the ideal of an isolated nerve-muscle preparation in man. Our testing technique was standardized in accordance with known features of human muscle physiology. Nerve stimulation was always at supramaximal intensity. Since the twitch response of a curarized muscle is not stable until 8 seconds after a prior stimulus, we separated tetanization from the preceding single test twitch by at least 10 seconds; the rate of tetanization is also important. As shown by Merton, nerve stimulation at rates of 40 per second or greater produces a maximal contraction, equal in strength to that developed during maximal voluntary contraction. At a rate of 40 per second, contraction of the muscles of the hand is well-sustained for at least 5 to 10 seconds. Hence we chose 5 seconds of tetanization as sufficient time to study muscle fatigue. Post-tetanic facilitation is most evident in the first 5 to 10 seconds following tetanization and probably reaches a maximum 2 seconds after tetanization. Our testing sequence was based on the latter observation.

Because of the associated discomfort, the muscle response to tetanization is rarely studied in unanesthetized man. The available reports show a well-sustained tetanic response,
and from 120 to 160 per cent post-tetanic facilitation in awake normal man.\textsuperscript{12, 13} \footnote{In one of us, following ulnar nerve block at the elbow, the tetanic tension ratio was 96 per cent and the post-tetanic tension ratio was 135 per cent.} We found similar values during halothane anesthesia. The tetanic tension ratio was always 95 per cent or greater (well-sustained) and post-tetanic facilitation remained between 100 and 150 per cent, in agreement with observations by Churchill-Davidson \textit{et al.}\textsuperscript{14} Neuromuscular transmission is apparently not affected by halothane in the concentrations used for clinical anesthesia. It is worth nothing here that our observation of a close association between EMG and tension in the unanesthetized subject holds true also during anesthesia, as well as during neuromuscular block. Thus, in testing for neuromuscular function, EMG and muscle tension may be used interchangeably.

We found no evidence of the reported dual mode of action of succinylcholine or decamethonium in man. Although a differentiation between phase I and phase II has a sound pharmacological basis,\textsuperscript{15, 16} these phases are, according to our results, indistinguishable by measurement of evoked, muscle responses. Neither is a clinical differentiation into depolarization, non-depolarization or desensitization block\textsuperscript{17} consistent with our findings. For lack of more precise terminology we believe it preferable to call the neuromuscular block observed here “succinylcholine block” as opposed to “curare block.”

Post-tetanic facilitation has frequently been used to diagnose the transition from phase I to phase II block.\textsuperscript{2, 5, 9} We saw significant post-tetanic facilitation (over 200 per cent) with small as well as large doses of succinylcholine and decamethonium. The magnitude was related solely to “depth” of neuromuscular block and not to drug dosage or length of drug administration. Hence testing for post-tetanic facilitation does not contribute to the identification of phase of neuromuscular block.

The above statements are not intended to denigrate the clinical value of monitoring neuromuscular transmission with a nerve stimulator; we merely point out the limitations of the method. The nerve stimulator has proven an excellent tool to monitor “depth” of muscular relaxation, and has been valuable in determining functional recovery of neuromuscular transmission. It has not, however, lived up to the expectation of identifying the shift from phase I to phase II neuromuscular block, nor the stage at which the block may be reversed by anticholinesterase drugs. This is in accordance with the findings by Gissen and his associates\textsuperscript{18} who showed that the reversibility of neuromuscular block is determined by plasma level of depolarizing agents, rather than by a particular pattern of response of the muscle.

\textbf{Summary and Conclusions}

Characteristics of the neuromuscular block during succinylcholine or decamethonium administration were studied in 32 patients anesthetized with halothane. Electromyogram (EMG) and isometric tension of the adductor pollicis brevis muscle, in response to electrical stimulation of the ulnar nerve, were recorded simultaneously.

From the onset of block, fade of EMG and fatigue of tension during tetany, and post-tetanic facilitation were noted. A phase I block, identified by well-sustained tetanic responses and absence of post-tetanic facilitation was never seen, not even with the smallest effective blocking doses of succinylcholine (10 mg.) or decamethonium (2 mg.).

The correlation between muscle fatigue and neuromuscular transmission and dose of drug was significant. Tetanic muscle fatigue increased progressively as more drug was given or as neuromuscular block became more profound. Post-tetanic facilitation on the other hand was related neither to drug dosage nor to duration of administration; it was related only to level of neuromuscular transmission. Since post-tetanic facilitation increases only as neuromuscular block becomes more profound it does not contribute to characterization of the neuromuscular block produced by depolarizing agents.

We conclude that phase I, phase II, and curare-type block cannot be differentiated clinically on the basis of muscle responses to nerve stimulation.
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References


Drugs

THIOPENTAL POTENTIATION Administration of tannic acid to rats as a retention enema prolonged the duration of anesthesia induced by thiopental given immediately before, or 72 hours after, the tannic acid. The dose of tannic acid given to the rats corresponded, on the basis of body weight, to a radiodiagnostics enema of 2 liters of 0.25 per cent tannic acid in barium sulfate suspension given to a child weighing 25 kg. By excluding certain hypothermic effects of tannic acid, it was concluded that thiopental potentiation was probably due to impairment by the tannic acid of the liver’s ability to detoxify the barbiturate. The results suggest that a drug which is detoxified in the liver should be administered 3 to 5 days after a tannic acid-barium sulfate radiodiagnostic enema only with considerable caution. (Singh, J., and Boyd, E.: Thiopenatal Anesthesia and Tannic Acid Diagnostic Enemas, Canad. Med. Ass. J. 95: 558 (Sept.) 1966.)