

Long-term Succinylcholine Infusion during Isoflurane Anesthesia

F. Donati, M.D., Ph.D.,* and D. R. Bevan, M.B., M.R.C.P., F.F.A.R.C.S.†

The characteristics of the neuromuscular blockade produced by prolonged succinylcholine infusion were compared in 40 patients anesthetized with either nitrous-oxide-isoflurane (0.75-1.50% inspired) or nitrous-oxide-fentanyl. Neuromuscular transmission was monitored using train-of-four stimulation and the infusion rate was adjusted to keep the first twitch at 10-15% of its control value.

Initially, all patients exhibited a depolarizing-type block, and the infusion rates were similar in the isoflurane ($61 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and fentanyl ($57 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) groups. Tachyphylaxis developed in both groups and correlated well with the onset of non-depolarizing (phase II) block. Both occurred sooner and at a lower cumulative dose in the isoflurane group. After 90 min, infusion rates were similar in both groups (isoflurane: $107 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; fentanyl: $93 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). After the infusion was stopped, the recovery of the train-of-four ratio was inversely related to the dose and duration of exposure to succinylcholine, and was slower with nitrous-oxide-isoflurane anesthesia. After 10 min of recovery, patients receiving isoflurane exhibited train-of-four ratios of 0.5 or less after 8.5 mg/kg succinylcholine and 103 min. Corresponding figures for fentanyl patients were 13 mg/kg and 171 min. The block in all 13 patients (eight with isoflurane, five with fentanyl) who did not recover spontaneously was antagonized successfully with atropine and neostigmine.

It was concluded that with succinylcholine infusion of 90 min or less, isoflurane accelerates the onset of tachyphylaxis and phase II neuromuscular block without affecting succinylcholine requirements. These results, with isoflurane, were similar to those reported previously with enflurane or halothane. (Key words: Anesthetics, volatile: isoflurane. Interactions (Drug). Measurement techniques: neuromuscular blockade. Neuromuscular relaxants: succinylcholine.)

INHALATIONAL ANESTHETIC AGENTS modify the characteristics of succinylcholine neuromuscular blockade.^{1,2} Using intermittent bolus injections of succinylcholine, Hilgenberg and Stoelting¹ found that the transition from phase I (depolarizing) block to phase II (nondepolarizing) block occurred at lower cumulative doses of succinylcholine during nitrous-oxide-halothane or nitrous-oxide-enflurane than nitrous-oxide-narcotic anesthesia. Donati and Bevan,² using a continuous infusion of succinylcholine, demonstrated that nitrous-oxide-enflurane, when compared with nitrous-oxide-narcotic anesthesia, accelerated the onset of phase II block, and delayed recovery, but succinylcholine was not potentiated during enflurane anesthesia.

The interactions between isoflurane and succinylcholine were studied by Miller *et al.*,³ who reported that isoflurane potentiated the neuromuscular blockade produced by bolus doses of succinylcholine. The effects of isoflurane on the transition from phase I to phase II block, on tachyphylaxis and on recovery were not examined.

The present investigation was undertaken to compare nitrous-oxide-isoflurane with nitrous-oxide-fentanyl anesthesia, with respect to the characteristics of the neuromuscular blockade produced by a continuous infusion of succinylcholine.

Methods

The protocol was approved by the Hospital Ethics Committee. After informed consent had been obtained, 40 healthy adult patients, ASA I or II, scheduled for elective general surgical procedures, with no known or suspected neuromuscular, hepatic, or renal disease, were assigned randomly to receive either nitrous-oxide-fentanyl or nitrous-oxide-isoflurane anesthesia. Patients in both groups were premedicated with 0.1 mg/kg morphine or 1 mg/kg meperidine and 0.4-0.6 mg atropine intramuscularly. Anesthesia was induced with 3-5 mg/kg thiopental and maintained with 70% nitrous oxide in oxygen. It was supplemented by isoflurane, 0.75 to 1.5% inspired, or fentanyl, 0.25 mg after induction, followed by 0.1 mg approximately every 30 min. All patients were intubated and they were ventilated to maintain normocapnia.⁴ Blood pressure and electrocardiogram were monitored in all cases.

Neuromuscular transmission was measured according to the method of Ali *et al.*⁵ The ulnar nerve was stimulated supramaximally at the elbow using subcutaneous needle electrodes. Trains-of-four with square pulses of 0.2 ms at a frequency of 2 Hz and a train duration of 2 s were repeated every 10 s using a Grass S48 stimulator and a SIU5 isolation unit. The hand and forearm were immobilized in a splint, and the force of adduction of the adductor pollicis was measured with a force-displacement transducer (Grass F.T.10) and recorded using a pen-and-ink recorder (Grass Polygraph). The temperature of the skin overlying the adductor pollicis was recorded and maintained above 34° C in all subjects.

After a stable baseline was obtained, a succinylcholine infusion (0.5%) was started using an infusion pump

* Resident.

† Associate Professor.

Received from the Departments of Anaesthesia, Royal Victoria Hospital and McGill University, 687 Pine Avenue West, Montreal, Quebec, Canada, H3A 1A1. Accepted for publication June 10, 1982.

Address reprint requests to Dr. Donati.

TABLE 1. Patient Data

	Patients		Succinylcholine	
	Age (yr)	Weight (kg)	Duration (min)	Dose (mg/kg)
Group 1—Fentanyl (9 men, 11 women)				
Mean	52.0	68.0	121	8.88
SEM	3.3	2.2	11	1.00
Range	21–80	50–85	60–225	2.9–18.6
Group 2—Isoflurane (9 men, 11 women)				
Mean	49.7	65.8	100	7.95
SEM	3.7	2.6	9	.91
Range	18–72	50–86	55–210	2.3–15.6

(IMED), at a rate of 10–15 mg/min. When the twitch response was abolished, the infusion rate was decreased and the trachea was intubated. The infusion rate of succinylcholine was then adjusted to keep the first twitch of the train-of-four at 10–15% of its preinfusion value. The infusion was stopped a few minutes before the anticipated termination of the operation, and the neuromuscular junction was allowed to recover spontaneously for 10 min. The train-of-four ratio, the ratio of the force of the fourth twitch to the force of the first twitch in each train, was then measured, and 1.25–2.5 mg neostigmine was given to patients whose train-of-four ratio was less than 0.5.

Infusion rates were calculated for every 10-min period after the start of the infusion. Time-response and dose-response curves were obtained according to the method of Litchfield and Wilcoxon.⁶ Mean values are presented with the standard error of the mean as an index of dispersion. Student's *t* test for unpaired data was applied where appropriate, and the null hypothesis was rejected when $P < 0.05$. Regressions were constructed by the least-squares regression method.⁷

Results

Both groups were comparable with respect to age, sex, weight, duration of infusion, and total dose of succinylcholine given (table 1).

INFUSION RATES

The mean succinylcholine infusion rates exhibited three characteristics (fig. 1). Both groups of patients showed: 1) an early decrease in succinylcholine requirement related to initial loading dose to establish the block; 2) a short stable period, and 3) a gradual increase in infusion rates (tachyphylaxis). In patients receiving isoflurane, this last phase occurred earlier. In the first 90 min of infusion, mean maintenance doses increased

from $57 \pm 4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $91 \pm 13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in patients given fentanyl, and from $61 \pm 5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $107 \pm 9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in patients receiving isoflurane. Neither the early nor late values were significantly different between the two groups of patients.

CHARACTERISTICS OF THE BLOCK

During the first few minutes of infusion, the train-of-four ratio was close to unity in all patients. Then, it decreased gradually, and this fade occurred sooner and developed more rapidly in patients receiving isoflurane (fig. 2). The differences between the two groups were statistically significant ($P < 0.05$) for train-of-four ratios of 0.5 or less.

Similarly, the cumulative succinylcholine dose required to achieve a given degree of train-of-four fade was smaller in patients who received isoflurane (fig. 3). The differences were statistically significant for train-of-four ratios of 0.25 and 0.

INFUSION RATE AND TRAIN-OF-FOUR RATIO

The relationship between infusion rates and the development of phase II block was studied by plotting the infusion rate which maintained first twitch height at 10% of control against the train-of-four ratio (fig. 4). As expected, the infusion rate increased with increasing fade in both the isoflurane and fentanyl groups. Furthermore, there was no statistically significant difference between the two groups.

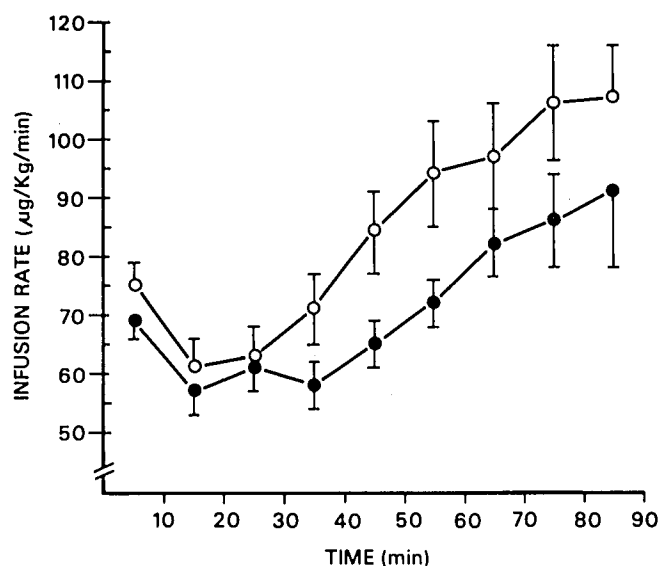


FIG. 1. Infusion rates of succinylcholine required to maintain 90% block in patients anesthetized with nitrous-oxide-fentanyl and nitrous-oxide-isoflurane. Bars indicate standard error of the mean. ○ = isoflurane; ● = fentanyl.

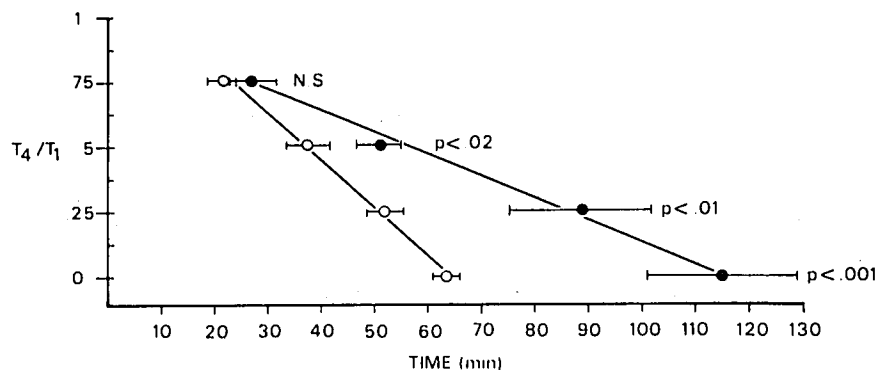


FIG. 2. Train-of-four ratio (T_4/T_1) versus time at which half the patients developed T_4/T_1 of 0.75, 0.5, 0.25, and 0, with nitrous-oxide-fentanyl and nitrous-oxide-isoflurane anesthesia. Bars indicate standard error of the mean. P values are as shown. N.S. = nonsignificant, i.e., $P > 0.05$. \circ = isoflurane, \bullet = fentanyl.

RECOVERY

After 10 min of spontaneous recovery, the train-of-four ratio related to the duration of the succinylcholine infusion and the total dose given. The recovery was slower with isoflurane than fentanyl anesthesia (figs. 5 and 6). For a train-of-four ratio recovery to 0.5, regression analysis showed an expected duration of succinylcholine infusion of 103 ± 10 min for isoflurane and 171 ± 22 min for fentanyl anesthesia, and expected doses of 8.5 ± 0.6 mg/kg and 13.0 ± 0.8 mg/kg, respectively. Both differences were statistically significant ($P < 0.01$). All patients (five fentanyl and eight isoflurane) who exhibited a train-of-four ratio of less than 0.5 after 10 min of spontaneous recovery were given neostigmine (1.25–2.5 mg) with atropine (0.6–1.2 mg), and this invariably produced recovery of the neuromuscular junction so that the train-of-four ratio exceeded 0.7 within 5 min.

Discussion

Isoflurane has been shown to potentiate the nondepolarizing neuromuscular blocking drugs *d*-tubocurarine, pancuronium, and gallamine.^{3,8} At comparable anesthetic concentrations, its effect at the neuromuscular junction is similar to enflurane,⁹ but both are more

potent than halothane. Miller *et al.*³ demonstrated a 33% decrease in the ED_{50} of succinylcholine during isoflurane anesthesia, using 1.25 MAC concentrations. No such potentiation was observed in this study, at least during the first 90 min of infusion. Many factors, such as the time and form of succinylcholine administration, and the difference in controls, might explain the discrepancy. In the study of Miller *et al.*,³ succinylcholine was given in a bolus form, at least 45 min after the onset of isoflurane anesthesia, which allowed equilibrium of the anesthetic with muscle, and the results were compared with those obtained with halothane. The present study was conducted with a continuous infusion of succinylcholine given from the onset to the termination of anesthesia and the effects of nitrous-oxide-isoflurane were compared with nitrous-oxide-fentanyl. Furthermore, muscle blood flow is increased by isoflurane anesthesia,¹⁰ and this would increase the dose of succinylcholine delivered to muscle after a bolus injection. However, during an infusion of succinylcholine, this effect is counteracted by the simultaneous increased removal of the drug from muscle, and this may explain the potentiation seen with bolus injections but not with a continuous infusion.

The succinylcholine requirements for a 90% block increased with time, with both isoflurane and narcotic

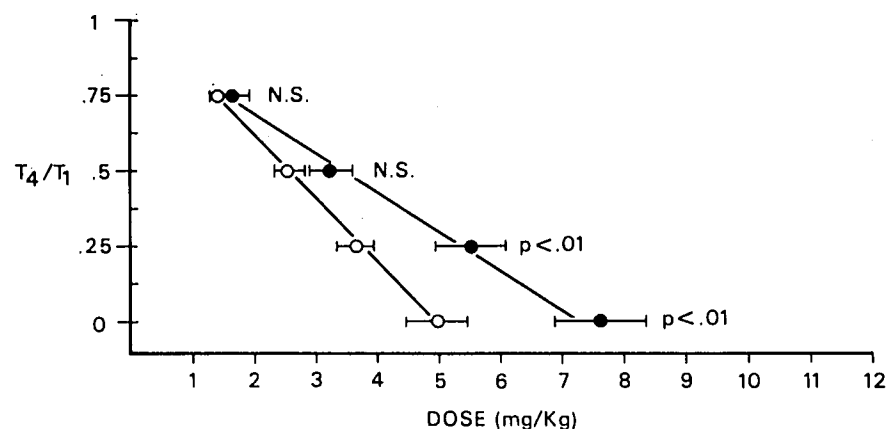


FIG. 3. Train-of-four ratio (T_4/T_1) versus cumulative dose necessary for half the patients to develop T_4/T_1 of 0.75, 0.5, 0.25, and 0, with nitrous-oxide-fentanyl and nitrous-oxide-isoflurane anesthesia. Bars indicate standard error of the mean. P values are as shown. N.S. = nonsignificant, i.e., $P > 0.05$. \circ = isoflurane; \bullet = fentanyl.

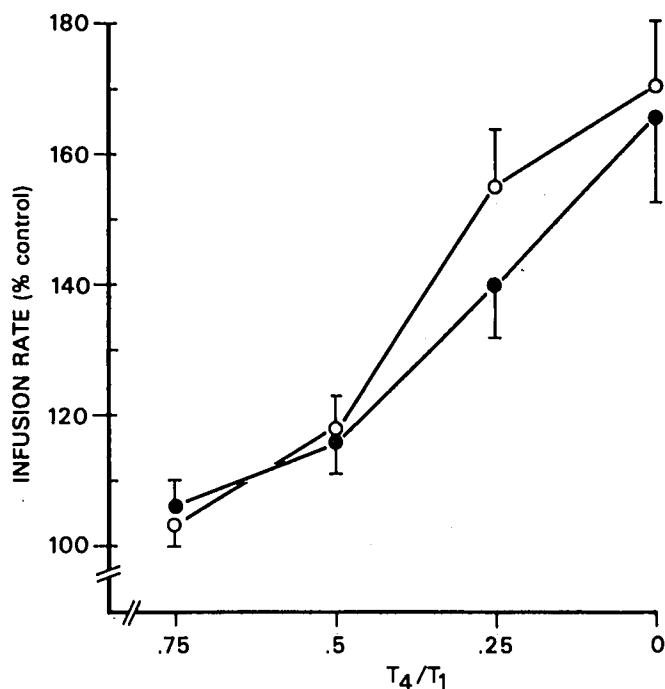


FIG. 4. Infusion rates, expressed as per cent control, necessary to keep 90% block *versus* train-of-four ratio (T_4/T_1). Control is the initial infusion rate between 10 and 30 min after the start. Bars indicate standard error of the mean. \circ = isoflurane; \bullet = fentanyl.

anesthesia. Infusion rates were similar in both groups of patients, both at the beginning of the infusion, when the block was mainly depolarizing, and 90 min later, when the block was mainly nondepolarizing. The increase may occur earlier with isoflurane anesthesia because phase II block develops earlier. In addition, if it is assumed that the phase II and phase I blocks are antagonistic, then the effect of isoflurane at the neuromuscular junction would be expected to add to the effects of phase II block. Consequently, isoflurane leads to more rapid onset of tachyphylaxis and more depression of the train-of-four ratio. These findings are similar to the effect of enflurane on succinylcholine block.²

The main effect of isoflurane on neuromuscular blockade was a significant acceleration of the development of nondepolarizing (phase II) block, characterized by decreasing train-of-four fade. In this respect, isoflurane behaves like enflurane: in a previous study,² a train-of-four ratio of 0.5 was reached after 31 min of succinylcholine infusion during enflurane anesthesia at a cumulative dose of 2.2 mg/kg, whereas with isoflurane, a train-of-four ratio of 0.5 was reached at 37 min and 2.7 mg/kg. The difference in the degree of fade between isoflurane and fentanyl anesthesia increases with time. For instance, both anesthetics produced a train-of-four ratio of 0.75 at about the same time, while the difference was quite marked for a train-of-four ratio

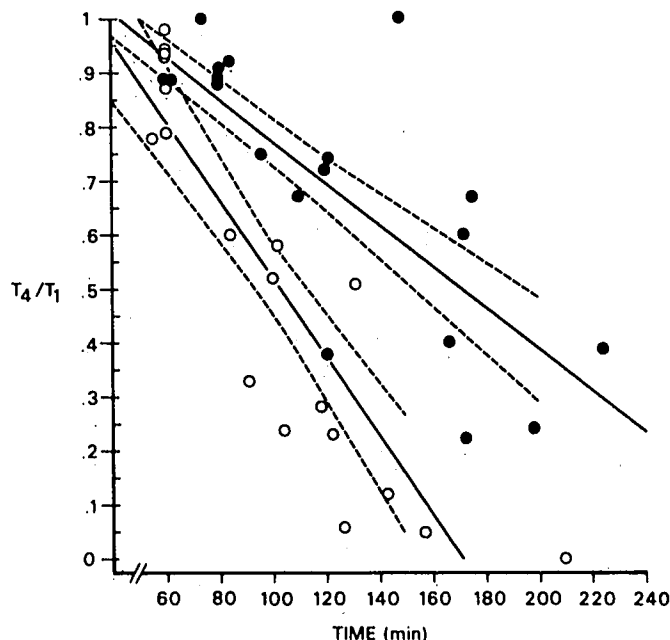


FIG. 5. Train-of-four ratio (T_4/T_1) after 10 min of spontaneous recovery *versus* total time of infusion in patients receiving fentanyl and isoflurane. Dashed lines represent one standard error of the mean. \circ = isoflurane; \bullet = fentanyl.

of 0 (fig. 2). This effect is due, at least in part, to the increase of isoflurane concentration in muscle tissue with time.¹¹

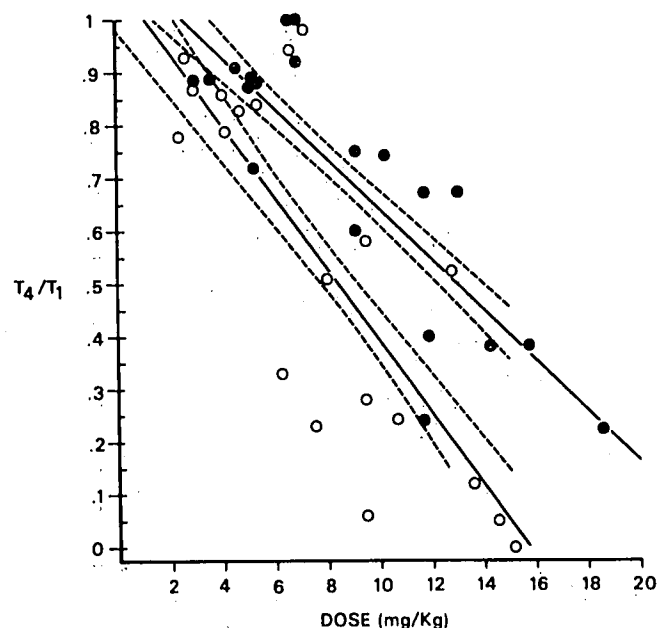


FIG. 6. Train-of-four ratio (T_4/T_1) after 10 min of spontaneous recovery *versus* total dose of succinylcholine in patients receiving fentanyl and isoflurane. Dashed lines represent one standard error of the mean. \circ = isoflurane; \bullet = fentanyl.

The present study gives additional indirect support for the relationship between tachyphylaxis and the change from phase I to phase II block. By considering tachyphylaxis and train-of-four fade as gradual, continuous processes, both phenomena were shown to be related. The same conclusion was reached previously for enflurane.^{2,12} It follows that because the change in block characteristics is observed later and is less predictable with nitrous-oxide-narcotic anesthesia,¹³ tachyphylaxis may not be seen, especially if the infusions are short and the level of neuromuscular block is low.

The rate of recovery of the train-of-four fade was inversely related to the total dose of succinylcholine and the duration of administration. However, isoflurane tends to shorten the duration and diminish the total dose required to achieve a given train-of-four ratio, 10 min after the infusion is stopped. In other words, the likelihood of observing a nondepolarizing (phase II) block after stopping the infusion is greater with isoflurane than narcotic anesthesia. However, in both isoflurane and fentanyl groups, all patients who showed a train-of-four ratio of 0.5 or less after 10 min of spontaneous recovery were given neostigmine, which increased the train-of-four ratio to 0.7 within 5 min. In this respect, enflurane and isoflurane behave similarly.²

It has been argued that the rapidity of onset of phase II block seen with inhalational anesthetic agents is a disadvantage, because succinylcholine can only be administered for a short time.¹ In fact, inhalational agents appear to have many advantages when used with succinylcholine. Because of its reversibility with anticholinesterase agents,^{2,14} phase II block does not need to be avoided. Furthermore, although the characteristics of the block generally change later with nitrous-oxide-narcotic anesthesia, this change is less predictable than with isoflurane. As a result, if one tried to determine a "safe period" during which phase II block does not occur in most patients, it would not be much different with both forms of anesthesia. Finally, a rapid transition from phase I to phase II block, as seen with inhalational

agents, can minimize the occurrence of "mixed" block, for which anticholinesterases are poorly effective.

References

1. Hilgenberg JC, Stoelting RK: Characteristics of succinylcholine-produced phase II neuromuscular block during enflurane, halothane, and fentanyl anesthesia. *Anesth Analg (Cleve)* 60:192-196, 1981
2. Donati F, Bevan DR: Effect of enflurane and fentanyl on the clinical characteristics of long-term succinylcholine infusion. *Can Anaesth Soc J* 29:59-64, 1982
3. Miller RD, Way WL, Dolan WM, Stevens WL, Eger EI: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. *ANESTHESIOLOGY* 35:509-514, 1971
4. Bain JA, Spoerel WE: Flow requirements for a modified Mapleson D system during controlled ventilation. *Can Anaesth Soc J* 20:629-636, 1973
5. Ali HH, Utting JE, Gray C: Stimulus frequency in the detection of neuromuscular block in humans. *Br J Anaesth* 42:967-978, 1970
6. Litchfield JT, Wilcoxon F: A simplified method of evaluating dose effect experiments. *J Pharmacol Exp Ther* 96:99-113, 1949
7. Dixon WJ, Massey FJ Jr: Introduction to Statistical Analysis. 3rd edition. New York, McGraw-Hill, 1969
8. Miller RD, Eger EI, Way W, Stevens WC, Dolan WM: Comparative neuromuscular effects of Forane and halothane alone and in combination with *d*-tubocurarine in man. *ANESTHESIOLOGY* 35:38-42, 1971
9. Fogdall RP, Miller RD: Neuromuscular effects of enflurane alone and combined with *d*-tubocurarine, pancuronium and succinylcholine in man. *ANESTHESIOLOGY* 42:173-178, 1975
10. Stevens WC, Cromwell TH, Halsey MJ, Eger EI, Shakespear TF, Bahlman SH: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. *ANESTHESIOLOGY* 35:8-16, 1971
11. Eger EI: *Anesthetic Uptake and Action*. Baltimore, Williams and Wilkins, 1974; pp 82, 88
12. 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
13. Ramsey FM, Lebowitz PW, Saverese JJ, Ali HH: Clinical characteristics of long-term succinylcholine neuromuscular blockade during balanced anesthesia. *Anesth Analg (Cleve)* 59:110-116, 1980
14. Lee C: Train-of-four fade and edrophonium antagonism of neuromuscular block by succinylcholine in man. *Anesth Analg (Cleve)* 55:663-667, 1976