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Dose–response Curves for Succinylcholine: Single Versus *Cumulative Techniques*

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This study was performed to determine the potency of succinylcholine using the single-dose technique, and to test the ability of the cumulative dose technique for generating dose–response data. Thirty-eight adult patients received single doses (n = 18), cumulative doses (n = 10), or cumulative doses of succinylcholine with an infusion to replace metabolized drug (n = 10). During opiate–thiopental–nitrous oxide anesthesia the force of contraction of the adductor pollicis in response to train-of-four stimulation was measured and recorded. Linear regressions were obtained between the logit transformation of neuromuscular blockade and log dose. Similar potencies were obtained with single dose and cumulative dose with infusion techniques with an ED_{90} of 0.27 ± 0.03 and 0.26 ± 0.02 mg/kg (mean ± SEM) respectively. However, cumulative dose without infusion significantly underestimated potency with an ED_{90} of 0.42 ± 0.06 mg/kg ($P < 0.05$ compared with the other two techniques). It is concluded that cumulative dose techniques can be accurately employed to determine the potency of succinylcholine if an infusion is utilized to compensate for eliminated drug. The data suggest that clinically used doses of succinylcholine (1.0–1.5 mg/kg) are equivalent to 3–5 times the ED_{90} and may explain the excellent intubating conditions provided by this drug. (Key words: Pharmacology: dose–response curves. Pharmacodynamics: succinylcholine.)

THE CONSTRUCTION of dose–response curves for neuromuscular blocking agents permits valid comparisons of the potencies among similar drugs. Although extensive data exist concerning dose–response relationships for nondepolarizing muscle relaxants (recently summarized by Shanks),[1] current data are limited for the depolarizing muscle relaxant succinylcholine. Such data are required to make useful comparisons between nondepolarizing agents and succinylcholine.

The traditional technique of determining dose–response relationships for neuromuscular blocking agents involves the random administration of a number of single predetermined doses to several patients. This single-dose technique has two major drawbacks: 1) the treatment of 0% and 100% neuromuscular depression is difficult on probit or logit scales, and 2) a large number of patients is required to produce statistically valid results. These disadvantages may be largely avoided if a cumulative dose technique is employed, and long-acting nondepolarizing muscle relaxants have been successfully studied using cumulative dose–response techniques.[2,3] However, the cumulative dose technique may underestimate potency for short or intermediate acting neuromuscular relaxants because of the relatively rapid elimination or redistribution of the drug during administration of incremental doses.[4–7] The cumulative dose technique may, however, be valid if an infusion is added to replace eliminated drug. This has been demonstrated for atracurium and vecuronium.[8] Succinylcholine is metabolized much more rapidly than these nondepolarizing relaxants. Thus, the importance of the infusion in the cumulative dose technique is expected to be greater.

The present study was designed to obtain dose–response relationships for succinylcholine in patients anesthetized with nitrous oxide–opiates. Three different techniques were used: single dose, cumulative dose, and a combination of cumulative dose with an infusion to replace drug lost by redistribution and/or metabolism.

Materials and Methods

After approval by the Hospital Ethics Committee, 38 adult patients (ASA P.S. I or II) scheduled for elective surgery were studied. Patients with hepatic, renal, or neuromuscular disease, or those taking medications known or suspected to interfere with neuromuscular transmission were excluded. Premedication consisted of oral diazepam (0.15 mg/kg) or an opiate (morphine 0.1 mg/kg or meperidine 1.0 mg/kg) with atropine 0.006 mg/kg intramuscularly. Arterial blood pressure was monitored with an automatic device (Dinamap®), and the electrocardiogram was displayed continuously. Anesthesia was induced with thiopental, 3–5 mg/kg, and maintained with nitrous oxide 66% in oxygen and supplemental doses of thiopental, 0.5–1.5 mg/kg, and fentanyl, 1–2 μg/kg, as required. Ventilation was assisted manually to maintain end-tidal carbon dioxide at 30–35 mmHg (mass spectrometer). No volatile agents were used.

The ulnar nerve was stimulated supramaximally at the elbow using train-of-four impulses 0.2 ms in duration delivered at a frequency of 2 Hz/12 s. The hand and forearm were immobilized in a splint. The force of contraction of the adductor pollicis muscle was mea-

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sured and recorded. After a stable baseline was obtained, single or cumulative doses of succinylcholine were administered in a random fashion as follows. Eighteen patients received succinylcholine in one of three doses (0.15, 0.20, or 0.25 mg/kg). Ten patients received initial doses of succinylcholine 0.15 mg/kg. Incremental doses of 0.1 mg/kg were then administered until at least 95% fourth twitch (T4) depression relative to control was observed. Each drug increment was given only after the effect of the previous dose had reached a stable response, defined as two equal consecutive T4. Ten patients received initial and incremental doses of succinylcholine as described for cumulative dose, but to allow for the rapid elimination of the drug an infusion was started once the response to the initial dose was stable. The rate of infusion required to replace drug lost by redistribution or metabolism was determined as follows: the dose of succinylcholine to maintain a constant 90% neuromuscular blockade by infusion is approximately 1.70–4.68 $mg \cdot kg^{-1} \cdot h^{-1}$,[9-12] and the ED_{90} for succinylcholine has been estimated at 0.22–0.30 mg/kg.[13] Assuming linear pharmacokinetics, the rate of elimination should be proportional to the dose given. Therefore, the hourly rate to maintain 90% blockade is approximately 15 times the ED_{90}, and the hourly rate at which succinylcholine should be administered to compensate for elimination is 15 times the dose already given. For example, when the maximum effect from the first dose of succinylcholine (0.15 mg/kg) was observed, a second dose (0.1 mg/kg) was administered and the infusion was commenced at 2.25 $mg \cdot kg^{-1} \cdot h^{-1}$ (15 times the initial dose). When the maximum blockade from the second dose was apparent, a third incremental dose (0.1 mg/kg) was given and the infusion was increased to 3.75 $mg \cdot kg^{-1} \cdot h^{-1}$ (15 times the cumulative dose already given). After a cumulative dose of 0.35 mg/kg, the infusion was set at 5.25 $mg \cdot kg^{-1} \cdot h^{-1}$. Thus, the infusion rate increased linearly with the amount of drug already given. Only the dose given in bolus form was considered in the calculations of dose–response curves because the amount given by infusion was only to compensate for drug elimination.

First twitch tension responses (T1) commonly exceed the baseline value when small doses of succinylcholine are employed.[14-16] Thus, logit transformation of T1 responses at the adductor pollicis was not possible. This twitch augmentation was much less apparent at T4. Consequently, T4 responses of the adductor pollicis muscle compared with prerelaxant control values were used as a measure of succinylcholine blockade to construct dose–response curves. Linear regressions were obtained between the logit transformation of T4 relative to control and the logarithm of the dose using the method of least-squares analysis.[17] To validate the use of T4 responses for the adductor pollicis, the linear neuromuscular responses (absolute percent depression, nontransformed data) for T1 and T4 relative to their respective controls were determined. For the single-dose technique each patient represented one data point, whereas for cumulative dose with and without an infusion, a regression line was calculated for each patient from which a mean dose–response curve was constructed. The accuracy of the cumulative dose techniques (with and without an infusion) for generating dose–response data was assessed by comparison with the traditional single-dose technique. The slope of the lines and ED_{50}, ED_{90}, and ED_{95} calculated from these regression lines were compared using a one-way ANOVA. When the F ratio was significant, the method of protected least significant difference was employed to identify differences between groups.[18] Patient demographic data were compared with chi-square and unpaired Student's t test. The results are presented as mean values ± SEM. A P value < 0.05 was considered significant.

TABLE 1. Demographic Data

	Single Dose	Cumulative Dose	Cumulative + Infusion
Males/females	7/11	4/6	3/7
Age (yr)	48 ± 4	52 ± 5	44 ± 5
Weight (kg)	68 ± 3	65 ± 4	66 ± 3

Values are given as mean ± SEM.

Results

Patient data are summarized in table 1. There were no significant differences between groups. A typical tracing obtained from a patient using the cumulative dose with infusion technique is shown in figure 1. The initial twitch augmentation is most apparent in T1 and almost nonexistent in T4. The tracing demonstrates the ability of the infusion to maintain a relatively stable degree of neuromuscular blockade. Augmentation of T1 relative to control occurred in nearly every patient (32 of 38) to an average of 133 ± 4%. The time to maximal T1 augmentation was 0.8 ± 0.04 min. Maximum blockade from the first dose occurred 1.4 ± 0.1, 1.3 ± 0.1, and 1.3 ± 0.1 min after injection in the single dose, cumulative dose, and cumulative dose + infusion groups, respectively.

Patients receiving simple cumulative dose regimens required more succinylcholine to produce equivalent blockade than patients receiving cumulative dose with infusion. The ED_{90} were 0.42 ± 0.03 and 0.26 ± 0.02

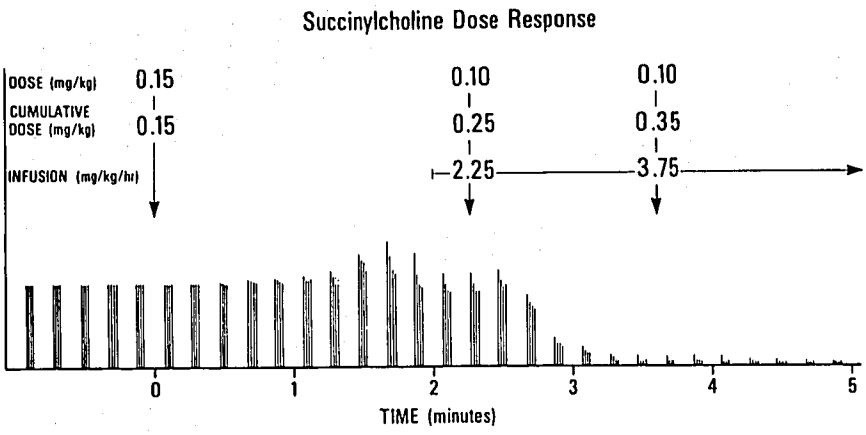

FIG. 1. Typical tracing of twitch tension using the cumulative with infusion technique. Succinylcholine, 0.15 mg/kg, was administered at time zero. After 1.6 min T1 height reached a maximum of 147% of control, but twitch augmentation was virtually absent from T4. Maximum effect from the first dose was observed at 2.2 min, at which time T4 height was 87% of prerelaxant control. A second dose of 0.1 mg/kg was administered, and an infusion was started (arrow). The second dose produced a minimum T4 height of 12% compared with presuccinycholine control. With a third dose 2% T4 height was achieved. In this patient calculated ED_{50}, ED_{90}, and ED_{95} were 0.19, 0.27, and 0.30 mg/kg, respectively.

mg/kg, respectively, $P < 0.05$ (table 2). This corresponded to more dose increments (3.9 ± 0.3 *vs.* 2.4 ± 0.2 doses, $P < 0.01$) and longer times to complete the study (5.5 ± 0.5 *vs.* 3.4 ± 0.3 min, $P < 0.01$). Thus, the cumulative dose–response curve was flatter and to the right of the single dose and cumulative dose with infusion curves (fig. 2), with statistically different ED_{90} and ED_{95} ($P < 0.05$, table 2). There were no significant differences in the ED_{50}, ED_{90}, or ED_{95} between single dose and cumulative dose + infusion (table 2).

If linear (nontransformed data) T1 relative to control was employed in the calculation of dose–response curves, the ED_{50} and ED_{90} values were 0.21 ± 0.02 and 0.35 ± 0.04 mg/kg for the single-dose technique, respectively. Corresponding values for cumulative dose were 0.26 ± 0.03 and 0.46 ± 0.07 mg/kg, and for cumulative dose + infusion were 0.17 ± 0.02 and 0.27 ± 0.02 mg/kg. Using linear T4 relative to control, the ED_{50} and ED_{90} for single dose were 0.19 ± 0.02 and 0.34 ± 0.05 mg/kg, respectively, 0.24 ± 0.02 and 0.42 ± 0.05 mg/kg for cumulative dose, and 0.15 ± 0.02 and 0.26 ± 0.02 mg/kg for cumulative dose + infusion. The slopes of the lines were similar between groups. There was no evidence of development of phase II block (defined as T4:T1 ratio < 0.5) in any patient. The total amount of succinylcholine received as infusion in the cumulative dose with infusion group was 0.08 ± 0.013 mg/kg, or 27 ± 3% of the cumulative dose.

Discussion

The present study demonstrates that the ED_{90} of succinylcholine during thiopental–nitrous oxide–fentanyl anesthesia is about 0.25–0.30 mg/kg, as determined by the single-dose or cumulative dose with infusion technique. This value is significantly less than that obtained with the cumulative dose technique without infusion. This is most likely because a considerable amount of drug is metabolized during the study period. Thus, the cumulative dose technique without infusion overestimates the amount of succinylcholine required to produce 50%, 90%, or 95% blockade by 26%, 56%, and 65%, respectively, when compared with the single-dose technique. However, the potency estimates with cumulative dose with infusion are similar to those obtained by the single-dose technique, suggesting that it is possible to use cumulative dose with infusion to generate satisfactory dose–response curves. The main advantages of the cumulative dose with infusion technique are that fewer patients are required to produce statistically reliable results and the treatment of 0% and 100% blockades (which may require elimination of data or an arc-

TABLE 2. Comparison of Cumulative and Single-Dose Techniques for Succinylcholine

	Single Dose	Cumulative Dose	Cumulative + Infusion	*F* Ratio	*P* Value
ED_{50} (mg/kg)	0.19 ± 0.02	0.24 ± 0.02*	0.17 ± 0.01	5.84	0.01
ED_{90} (mg/kg)	0.27 ± 0.03	0.42 ± 0.06†	0.26 ± 0.02	5.45	0.01
ED_{95} (mg/kg)	0.31 ± 0.04	0.51 ± 0.08†	0.30 ± 0.03	4.89	0.02

Values are given as mean ± SEM.

* $P < 0.05$, cumulative dose *versus* cumulative + infusion techniques.

† $P < 0.05$, cumulative dose *versus* single dose and cumulative plus infusion techniques.

sine transformation to finite values) that may be produced by single doses is avoided.

The cumulative dose with infusion technique requires prior knowledge of the ratio of the dose needed to establish blockade to the infusion rate to maintain this blockade constant. The actual level of blockade obtained is not important. In this study the ratio was determined from previous estimates of ED_{90} and the infusion rate to maintain 90% blockade. If these data had not been available, one would need to give a predetermined dose, *e.g.*, 0.2 mg/kg, wait until maximum blockade, and then start an infusion to maintain blockade constant. From the results obtained in a few patients, the infusion rate:dose ratio could be calculated. Thus, although the response to one dose is required before one can apply the cumulative dose–response with infusion technique, one does not need prior knowledge of the full dose–response relationship.

However, it may sometimes be necessary to obtain potency measurements even if dose–response relationships have been determined previously. Such situations arise while studying the effect of inhalational anesthetics, chronic medication, or coexisting disease on the potency of an neuromuscular blocking drug. The cumulative dose with infusion technique is also useful to examine the sensitivity of two or more different muscles in the same individual.

Our estimates of ED_{50} and ED_{90} from either the single-dose or cumulative dose with infusion techniques were greater than those obtained by Miller *et al.*[19] who compared the dose–response relationships for succinylcholine during 1.25 MAC isoflurane and halothane anesthesia using single twitch tension. Their ED_{50} values during isoflurane and halothane anesthesia were 3.4 and 5.1 mg/m^2, respectively. This corresponds to approximately 0.09 and 0.13 mg/kg, respectively, assuming a surface area of 1.81 m^2 and a weight of 70 kg. Corresponding values for ED_{90} during isoflurane and halothane anesthesia were 0.13 and 0.18 mg/kg, respectively. However, they did not mention twitch augmentation, which can alter potency estimates, nor did they utilize logit or probit analysis of neuromuscular block. Furthermore, to obtain a sufficient number of data points, each patient received three different doses during the same anesthetic after allowing for suitable recovery from the effects of the previous dose. This may introduce some degree of bias to the results because the previous dose of relaxant may have altered the sensitivity of the neuromuscular junction despite return of twitch height to control values. Also, twitch tension commonly surpasses control values following recovery from succinylcholine.[14,16,20] Nevertheless, their data suggest that isoflurane potentiates the neuromuscular blocking effect of succinylcholine when compared

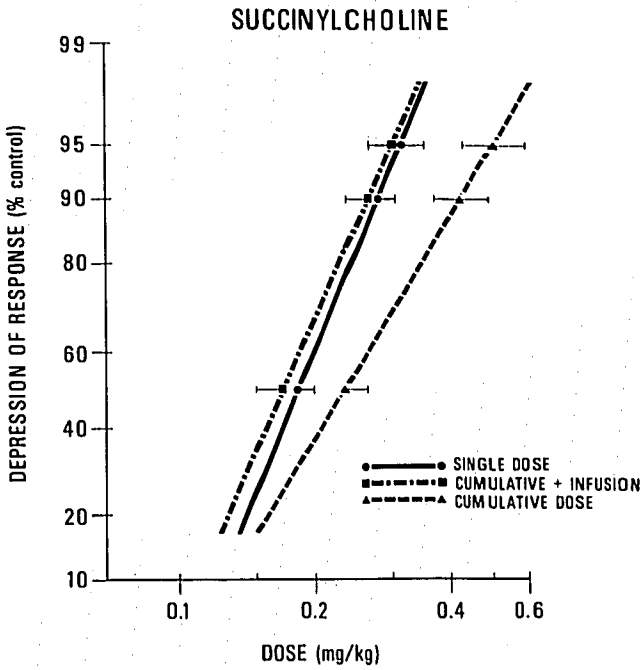

FIG. 2. Dose–response relationships for succinylcholine as determined by single dose, cumulative dose, or cumulative dose + infusion techniques. The logit transformation of T4 depression relative to control is plotted as a function of log dose. The lines were derived using linear regression. Error bars represent SEM.

with that of halothane. The potency estimates obtained in the present study are also less than those obtained by Cook *et al.*[13] who found the ED_{50} and ED_{90} to be 0.15 and 0.22 mg/kg, respectively. Their methodology involved the extrapolation of data obtained in previous studies[9,21] back to time zero assuming first-order elimination. This method may introduce a certain degree of error because time to recovery and not degree of blockade is measured, and extrapolations are made to time zero, not to time of maximum blockade. Furthermore, the model does not take into account the recovery of succinylcholine twitch tension to values greater than control.

The consistent observation that twitch tension increases after small doses of depolarizing muscle relaxants has been demonstrated previously for succinylcholine[14–16] and for decamethonium[22,23] and most likely represents repetitive firing at the neuromuscular junction.[15,24] This phenomenon is also seen in animals after neostigmine and may represent presynaptic activity.[25] The degree of twitch augmentation in the present study was such that if linear T1 values were used to calculate dose–response relationships, ED_{50} and ED_{90} potency estimates derived from the single dose-technique would be increased by 14% and 22%, respectively, compared with logit T4 values. Corresponding alterations in po-

tency estimates for cumulative dose with and without an infusion are less (2–8%), presumably because multiple data points were obtained from each patient until at least 95% depression of response was observed, and twitch augmentation was less noticeable with time. There was little difference in potency estimates obtained with either logit or linear T4 data, presumably because many data points were in the linear 20–80% response range. If several points had occurred in the asymptotes of the sigmoid curve, the differences would have been larger. Because succinylcholine acts *via* a depolarizing mechanism and fade is not observed until phase II block occurs, twitch tension values obtained for T4 are valid. The highest cumulative dose of succinylcholine used to produce at least 95% neuromuscular blockade in the present study was 0.65 mg/kg, a value not reported to cause phase II block in normal individuals.[9–11,26]

In conclusion, the present study demonstrates that the cumulative dose with infusion technique is valid for generating dose–response data for short-acting muscle relaxants. Fewer patients are required to produce valid, reliable results, and the problem of whether to include or reject blockades of 0% and 100% is avoided. This technique also has the unique advantage of allowing comparisons of muscle groups of differing sensitivities in the same patient. The data suggest that the doses used clinically for tracheal intubation in adults (1.0–1.5 mg/kg) are equivalent to 3–5 times the ED_{90} and may explain the excellent intubating conditions provided by succinylcholine.

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