A defasciculating dose of d-tubocurarine causes resistance to succinylcholine

James B. Eisenkraft MD MRCP FFARCS,
Melinda L. Mingus MD, Andrew Herlich DMD MD,
W. Jeffrey Book MD FRCPC, Aaron F. Kopman MD*

Forty-four patients, ASA physical status I or II, undergoing thiamylal, fentanyl, N₂O/O₂ anaesthesia were studied to determine the dose-response to succinylcholine (Sch) without prior defasciculation (24 pt – Group 1), or three minutes following d-tubocurarine (dTC), 0.043 mg · kg⁻¹ (20 pt – Group 2). The individual log dose-logit response curve for each patient was determined using a cumulative dose plus infusion technique and integrated EMG monitoring of the first dorsal interosseous muscle. The mean (± SEM) ED₅₀, ED₉₀ and ED₉₅ values for Sch in Group 1 were 0.13 ± 0.01, 0.19 ± 0.01 and 0.22 ± 0.01 mg · kg⁻¹, and in Group 2 were 0.16 ± 0.01, 0.25 ± 0.01 and 0.29 ± 0.02 mg · kg⁻¹, respectively. The mean ED values in Group 2 were significantly greater than the equivalent values in Group 1 (*P* < 0.05). Compared with values in Group 1, ED values in Group 2 represented mean increases of 23, 32, and 32 per cent, respectively. These pharmacodynamic data indicate that the dose of Sch needs to be increased by 32 per cent following a defasciculating dose of dTC 3 mg · 70 kg⁻¹ (0.043 mg · kg⁻¹).

Lors d'une anesthésie au thiamylal, fentanyl et N₂O, nous avons évalué la courbe dose-réponse de la succinylcholine (Sch) de 24 patients sans précurarisation (groupe 1) et celle de 20 autres, trois minutes après l'injection de 0,043 mg · kg⁻¹ de d-tubocurarine (groupe 2). Les mesures individuelles combinaient le

logarithme de la dose cumulative (infusion continue) au logit de la dépression de l'EMG du premier muscle interosseux dorsal. Les DE₅₀, DE₉₀ et DE₉₅ (moyenne ± erreur-type) de la Sch étaient respectivement dans le groupe 1 de : 0,13 ± 0,01, 0,19 ± 0,01 et 0,22 ± 0,01 mg · kg⁻¹ alors que dans le groupe 2 elles étaient de : 0,16 ± 0,01, 0,25 ± 0,01 et 0,29 ± 0,02, supérieures donc à celles du groupe 1 de 23, 32 et 32 pour cent respectivement (*P* < 0,05). Grâce à cette étude pharmacodynamique, on voit qu'il faut augmenter la dose de Sch de 32 pour cent si on la fait précéder d'une dose de 3 mg · 70 kg (0,043 mg · kg⁻¹) de d-tubocurarine.

The clinical dose of a muscle relaxant is usually selected on the basis of the effective dose (ED). Thus an ED₉₀ dose or multiple thereof would be administered to achieve relaxation for tracheal intubation. The ED₉₀ for succinylcholine (Sch) is 0.22–0.30 mg · kg⁻¹ and the commonly used intubating dose is therefore three to five times this value.¹

The administration of Sch is often preceded by a small dose of d-tubocurarine (dTC), which may prevent some of the undesirable side effects of Sch. Previous studies have suggested that the onset of relaxation produced by Sch is delayed and that the intensity and duration of relaxation are decreased following a defasciculating dose of dTC, but that adequate relaxation can be restored by increasing the usual dose of Sch by 25–75 per cent.^{2–5} Bevan *et al.*⁶ have recommended the use of Sch in a dose of 1 mg · kg⁻¹ when given alone, and 1.5 mg · kg⁻¹ when preceded by dTC. While previous studies have addressed the effect of dTC on the times to onset and offset of action of Sch, other than in terms of intubating conditions, the effect on the intensity of block has not been well documented. The purpose of this study was to document the effect of a small commonly used clinical dose of dTC, 3 mg · 70 kg⁻¹, on the dose-effect relationship of subsequently administered Sch.

Methods

Forty-four adult patients, ASA physical status I or II, scheduled to undergo elective orthopaedic or gynaecolog-

Key words

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From the Departments of Anesthesiology, Mount Sinai School of Medicine of the City University of New York, and Long Island Jewish Medical Center, New York*.

Address correspondence to: Dr. J.B. Eisenkraft, Department of Anesthesiology, Box 1010, The Mount Sinai Hospital, One Gustave L. Levy Place, New York, NY, 10029-6574 U.S.A.

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ical surgery gave written informed consent to participate in this institutionally approved study. All were free from drugs or conditions known to affect neuromuscular function. All patients received diazepam, 5–10 mg PO, as premedication prior to arrival in the operating room. Arterial blood pressure (Dinamap®), electrocardiogram and arterial haemoglobin oxygen saturation by pulse oximetry were continuously monitored in all cases. Anaesthesia was induced with thiamylal sodium, 3–5 mg · kg⁻¹ and maintained with nitrous oxide 66 per cent in oxygen. Supplemental doses of thiamylal 0.5–1.0 mg · kg⁻¹, and fentanyl, 1–2 µg · kg⁻¹, were administered as required. Ventilation was assisted using a bag and facemask to maintain end-tidal CO₂ within normal range (30–35 mmHg) as measured by mass spectrometry (Perkin Elmer Advantage 1100, Pomona, CA). Potent inhaled volatile anaesthetic agents were not used during the period of this study.

Neuromuscular transmission was assessed using an integrated EMG monitor (Datex NMT Monitor 221, Puritan Bennett, Wilmington, MA). Once the patient was anaesthetized as described above, supramaximal trains-of-four stimuli (2 Hz, stimulus duration 0.1 msec) were applied every ten seconds via surface electrodes to the ulnar nerve at the wrist and the baseline integrated EMG responses of the first dorsal interosseous muscle were recorded continuously. Following stabilization of the EMG response, the monitor was recalibrated to read a baseline EMG response of 100 per cent. At this time, 24 patients (Group 1) received no d-tubocurarine (dTC), while 20 patients (Group 2) received dTC 3 mg · 70 kg⁻¹ (0.043 mg · kg⁻¹). Three minutes later all patients received Sch 0.10 mg · kg⁻¹ IV followed by incremental doses of 0.05 mg · kg⁻¹ together with an infusion of Sch, the rate of which was adjusted to replace eliminated drug.⁷ Incremental doses were given and the infusion rate increased when two consecutive equal first responses (T₁/C) were observed in the continuously recorded EMG tracing. This cumulative dose plus infusion technique and the calculation of the rate of infusion needed with each incremental dose are described in detail elsewhere.⁷ Based upon the work of Smith *et al.*,⁷ it was assumed that if a given bolus dose of Sch produced a certain amount of depression T₁/C response, then an infusion rate of 15 times this dose per hour would be required to maintain that same level of T₁/C depression. Thus, following an initial bolus dose of Sch, 0.10 mg · kg⁻¹, when the T₁/C decrement had been stable for 20–30 seconds (three equal consecutive T₁/C responses), an incremental bolus dose of Sch 0.05 mg · kg⁻¹ was given and an infusion of (15 × 0.10) mg · kg⁻¹ · hr⁻¹ was commenced. With the administration of a further incremental bolus dose of Sch 0.05 mg · kg⁻¹, the infusion rate was increased to 15 × 0.15

mg · kg⁻¹ · hr⁻¹. Additional bolus doses of Sch and infusion rate increases were continued until a 95–99 per cent decrease in T₁/C had been achieved. At this time the trachea was intubated and the lungs were ventilated using an anaesthesia ventilator.

Regression analyses (least squares) were performed for each patient data set between the logit transformation of neuromuscular blockade (defined as percentage decrease in T₁/C) and the logarithm of the cumulative dose of Sch. Only the doses given in bolus form were considered in the calculation of the dose–response curves because the amount given by infusion was to compensate for drug which had been eliminated.⁷ From the individual dose–response curves, a mean dose–response curve was constructed for each group and from these the doses producing 50, 90, and 95 per cent block (ED₅₀, ED₉₀, and ED₉₅) were calculated. The group mean slopes, intercepts and ED values were compared using a Student's *t* test for unpaired data. The ED results are expressed as group means together with 95 per cent confidence limits. A difference in ED values between the two groups was considered to be significant if *P* was less than 0.05.

Results

Patient demographic data are summarized in Table I. No significant differences were found between the two groups in mean age or weight. In Group 2, three minutes following dTC the mean ± SD decrease in T₁/C was 5.3 ± 4.4 per cent. Each patient received between three and seven doses of Sch and the total duration of the study period in each patient was generally less than five minutes.

The mean dose–response curves derived from the individual patient data are depicted in the Figure. The curve for Group 2 (defasciculated) was to the right of that of Group 1. While no significant difference in slopes was found (*P* = 0.20), there was a significant difference in intercepts (*P* < 0.05). There were significant differences between the two groups in the ED₅₀, ED₉₀ and ED₉₅ values derived from these mean curves (Table II). The mean ED₅₀, ED₉₀ and ED₉₅ values in the defasciculated patients, Group 2, were 0.16, 0.25 and 0.29 mg · kg⁻¹,

TABLE I Demographic data

	Group 1 Sch n = 24	Group 2 dTC + Sch n = 20
Males/females	3/21	4/16
Age (yr)	37 ± 9	37 ± 8
Weight (kg)	65 ± 12	62 ± 9

Values are given as mean ± SD.

FIGURE Mean dose-response relationships for Sch administered alone and following dTC $0.043 \text{ mg} \cdot \text{kg}^{-1}$ as derived by a cumulative dose plus infusion technique.⁷ The logit transformation of T_1 depression per cent, as measured by integrated EMG, is plotted as a function of log cumulative dose. The lines were derived using linear regression (least squares). The equations to the lines are: Group 1 (Sch alone): logit response = $6.60 \times \log \text{dose} + 5.48$; Group 2 (dTC + Sch): logit response = $5.63 \times \log \text{dose} + 4.35$.

compared with 0.13 , 0.19 and $0.22 \text{ mg} \cdot \text{kg}^{-1}$ in the non-defasciculated patients, Group 1, respectively. On average, defasciculation caused a 23, 32 and 32 per cent increase in ED_{50} , ED_{90} and ED_{95} , respectively, when compared with controls.

Discussion

A defasciculating or "precurarizing" dose of d-tubocurarine (dTC) is commonly administered prior to succinylcholine (Sch) in order to prevent potentially undesirable effects, such as fasciculations, increased intragastric pressure, increased intraocular pressure, muscle pains and hyperkalaemia.⁸ An antagonism between the neuromuscular blockade produced by depolarizing and nondepolarizing relaxants was first described in 1949 in relation to dTC and decamethonium.⁹ Walts and Dillon¹⁰ studied the effect of dTC given three minutes before Sch and found significant reductions in both duration and intensity of the induced block. Miller and Way⁸ found that Sch $1.0 \text{ mg} \cdot \text{kg}^{-1}$ always produced 100 per cent twitch height depression, even when preceded by dTC 3 mg but that the time to 80 per cent recovery was shortened by dTC.

Cullen⁴ found that, when dTC 3 mg preceded Sch $1.0 \text{ mg} \cdot \text{kg}^{-1}$, the onset of block was delayed, the recovery time was shorter, and tracheal intubation was more difficult compared with Sch given alone. When the dose of Sch was increased to $1.5 \text{ mg} \cdot \text{kg}^{-1}$, intubating conditions were still not comparable with those in the control group. Freund and Rubin³ concluded that, if a 3 mg

TABLE II ED values ($\text{mg} \cdot \text{kg}^{-1}$) for non-defasciculated and defasciculated patients

	Group 1 Sch <i>n</i> = 24	Group 2 dTC + Sch <i>n</i> = 20	<i>P</i>
$\text{ED}_{50} \text{ mg} \cdot \text{kg}^{-1}$ (95 per cent confidence limits)	0.13 0.11–0.15	0.16 0.14–0.19	<0.05
$\text{ED}_{90} \text{ mg} \cdot \text{kg}^{-1}$ (95 per cent confidence limits)	0.19 0.17–0.22	0.25 0.22–0.28	<0.001
$\text{ED}_{95} \text{ mg} \cdot \text{kg}^{-1}$ (95 per cent confidence limits)	0.22 0.20–0.25	0.29 0.26–0.33	<0.001

defasciculating dose of dTC is used, "then at least 70 per cent more succinylcholine must be given to ensure consistently adequate relaxation for intubation."

Commenting on the above three studies,^{3,4,8} Miller² concluded that "paralysis by Sch will be decreased when it is preceded by 3 mg of dTC," and that, "in a 70 kg patient, the usual dose of Sch of about 60 mg would have to be increased to 100 mg" (i.e., by 66 per cent). Others have recommended Sch $1.0 \text{ mg} \cdot \text{kg}^{-1}$ given alone, and $1.5 \text{ mg} \cdot \text{kg}^{-1}$ when it is preceded by dTC.⁵ Ferguson and Bevan¹¹ found that dTC 3 mg, given before Sch $1.0 \text{ mg} \cdot \text{kg}^{-1}$, produced no observable difference in the intensity of the block because the twitch response was completely abolished in all but four of the 70 patients in their study. Intubating conditions were satisfactory in all of their patients, but this may have been due to their use of halothane 1.0–1.5 per cent for up to 20 minutes prior to intubation.¹¹

Only one study, that of Pauca *et al.*,⁵ has quantified the effect of pretreatment with dTC 3 mg on relaxation produced by subsequently administered Sch. However, in their study, Sch was given as a constant infusion ($0.58 \text{ mg} \cdot \text{sec}^{-1}$). In control patients (no dTC) the infusion times to achieve 50 and 90 per cent block were 34.7 and 46.0 sec, representing mean "infusion" ED_{50} and ED_{90} values of 0.34 and $0.46 \text{ mg} \cdot \text{kg}^{-1}$, respectively. Following a defasciculating dose of dTC 3 mg, $0.051 \text{ mg} \cdot \text{kg}^{-1}$, the mean infusion times to 50 and 90 per cent block were 46.3 and 58.3 sec, representing increases of 33 and 27 per cent in infusion times. The "infusion" ED_{50} and ED_{90} values of 0.45 and $0.57 \text{ mg} \cdot \text{kg}^{-1}$, represented increases of 29 and 18 per cent over control, respectively. The ED values calculated from Pauca *et al.*'s infusion data are greater than those reported by others who used different methods for potency estimation.^{7,12} They concluded that "a recommendation that dTC be given to block the side-effects of Sch is made with the accompanying

warning that 70–75 per cent more Sch is required for the same degree of block.”⁵ Others have suggested that dTC 3 mg pretreatment to prevent postoperative myalgias necessitated the use of only 25 per cent more Sch infusion to achieve comparable relaxation.¹³

In view of the above-described and sometimes conflicting reports on the effects of defasciculation, we sought to determine how the commonly used dose of dTC 3 mg (per 70 kg) would alter the dose–response to Sch administered three minutes later. Resistance in our study was defined as a significant increase in ED values. We used a cumulative dose plus infusion (CDI) technique to define the dose–response relationships for Sch. This technique has been shown to provide ED values for Sch which are essentially identical to those derived using a single dose technique, yet it offers the advantage that a complete dose–response curve can be obtained for each individual patient.^{7,12}

Potential problems with the use of a CDI technique to develop a dose–response relationship for Sch following dTC include that, while the first dose of Sch was given three minutes following dTC, the last was given some eight minutes after dTC. However, a pharmacokinetic model suggests that a fairly constant concentration of dTC would have been maintained in the effect compartment for the duration of the study period and therefore that the effect due to dTC should have remained constant.

Another potential problem is that the same Sch infusion rate (i.e., 15 times the cumulative dose given per hour) was used in all the cases studied and that it may have represented an excessive amount in some cases and too little in others. In the original description of the CDI technique the factor of 15 was used in each of the ten patients studied and derived ED data were essentially identical to those obtained in 18 patients in whom a single bolus technique was used.⁷ It is also likely that any such errors in infusion rate would have become unimportant when the mean for each group of patients was calculated.

We found that dTC 0.043 mg · kg⁻¹ increased the ED₅₀, ED₉₀, and ED₉₅ values for Sch by 23, 32 and 32 per cent, respectively. This is qualitatively in agreement with results of the studies previously cited.^{2–5,8,10} Quantitative differences are most likely due to differences in methodology between the present and previous studies. Thus while others have used single dose (1.0 vs 1.5 mg · kg⁻¹; 0.7 vs 1.2 mg · kg⁻¹)^{2,3} or infusion⁵ techniques to study the potency of Sch, we have defined the actual dose–response curves. It remains to be determined whether increasing the clinically used dose of Sch (usually 1 mg · kg⁻¹) by only 32 per cent, as is suggested by the present results, would restore to normal the onset and duration of Sch following defasciculation with dTC 3 mg.

Although the evoked mechanomyographic (MMG) response of the adductor pollicis muscle is the method

whereby neuromuscular blockade is most commonly monitored, Kopman¹⁴ has reported that the first dorsal interosseous EMG may be used interchangeably with adductor pollicis MMG in determining the depth of non-depolarizing neuromuscular blockade. We used integrated EMG monitoring of the first dorsal interosseous muscle because this technique is simple to apply and may also be used in patients whose arms need to be kept adducted. Furthermore, there does not appear to be an important difference between EMG T₁/C and MMG T₁/C when studying the onset of Sch-induced blockade although the EMG has been found to be depressed slightly more than the MMG.¹⁵ However, the relationship between the two monitoring techniques is linear¹⁵ and, since the EMG was used in all of our patients, we believe that a between-group comparison is therefore valid.

The ED values presently reported for Sch in normal patients are lower than those reported previously.¹² These differences are most likely due to the use of the first dorsal interosseous muscle in the present study, whereas previously the responses from the hypothenar muscles were monitored. That the first dorsal interosseous muscle may be more sensitive to the effects of non-depolarizing neuromuscular blocking drugs than are the hypothenar and adductor pollicis muscles has been suggested.¹⁶

In conclusion, we have shown by a cumulative dose plus infusion technique that the administration of dTC 3 mg · 70 kg⁻¹ significantly alters the dose–effect relationship for Sch administered three to eight minutes subsequently. Following dTC, the ED₅₀, ED₉₀ and ED₉₅ of Sch were increased by 23, 32 and 32 per cent, respectively. Previous studies have shown that dTC 3 mg slows the onset and speeds the offset of action of Sch, and recommendations have been to increase the Sch dose from 1.0 mg · kg⁻¹ to 1.5 mg · kg⁻¹ or by 25–75 per cent, following dTC. If the dose of Sch required to produce good conditions for tracheal intubation is a fixed multiple of the ED₉₀ then, based upon our results, the clinical dose of Sch should be increased by 32 per cent following defasciculation with dTC 0.043 mg · kg⁻¹. The mechanism whereby dTC causes resistance to subsequently administered Sch is not known, but it has been suggested that a defasciculating dose of the dTC binds to a number of the cholinergic receptors, thereby preventing Sch from reaching them.¹⁷

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