Anesthesiology
69:604-607, 1988

The Effects of Succinylcholine on Doxacurium-induced Neuromuscular Blockade

JEFFREY A. KATZ, M.D.,* ROBERT J. FRAGEN, M.D.,† COLIN A. SHANKS, M.D., CH.B.,‡
KAREN DUNN, R.N.,§ BARBARA MCNULTY, M.P.H.,¶ G. DAVID RUDD, M.S.**

Doxacurium (formerly BW A938U) is a new long-acting non-depolarizing skeletal muscle relaxant with a benzylisoquinolinium molecular structure similar to that of atracurium. Doxacurium's duration of action, however, resembles that of d-tubocurarine and pancuronium.[1,2] Unlike the long-acting non-depolarizing relaxants in clinical use, doxacurium appears devoid of cardiovascular side effects in humans.[1,2] It, therefore, might be potentially useful for the patient whose cardiovascular function is compromised and who is to undergo prolonged surgery.

Because approximately 4 min are required to achieve conditions adequate for tracheal intubation,[3] even if a dose of doxacurium as large as twice the ED_{95} is administered, its use is likely to be preceded by succinylcholine. Previous studies examining the effects of succinylcholine on subsequent doses of non-depolarizing relaxants showed potentiation, antagonism, or no effect, depending on the study design.[4-9] This study evaluates neuromuscular blockade produced by doxacurium when administered at 10% and 95% recovery from succinylcholine.

METHODS AND MATERIALS

Twenty-seven ASA physical status 1 or 2 adults gave institutionally approved written informed consent. Patients were 18 to 70 yr of age, 40–100 kg (table 1), and scheduled for elective surgical procedures. Excluded were female patients of child-bearing potential; patients with clinical or biochemical evidence of cardiac, renal, hepatic, neuromuscular, or psychiatric disease; and patients receiving quinidine, lidocaine, trimethaphan, phenytoin, or aminoglycoside antibiotics prior to the study period.

For all patients, anesthesia was induced intravenously with thiopental, 4–5 mg/kg, and fentanyl, 2–12 μg/kg. Anesthesia was maintained with 67% nitrous oxide in oxygen, supplemented by intravenous administration of fentanyl, thiopental, and droperidol given as indicated by responses to surgical stimulation. Ventilation was controlled to keep the end-expired P_{CO_2} between 32 and 38 mmHg as determined by mass spectrometry. Nasopharyngeal temperatures were maintained above 35° C. Tracheal intubation was facilitated by application of topical lidocaine.

Following induction of anesthesia, a Grass S-48 neuromuscular stimulator with an SIU5 isolation unit provided supramaximal square wave stimuli of 0.2 msec duration in a train-of-four pattern (2 Hz over 2 s) repeated every 12 s. Stimuli were applied by surface electrodes to the ulnar nerve at the wrist. The intensity of neuromuscular blockade was determined by measuring the force of thumb adduction in response to stimuli with a Devices ST-10 linear force transducer fixed to an armboard and attached to the thumb with a preload of about 300 g. Responses to stimulation were recorded on a Hewlett Packard® polygraph. Percent neuromuscular blockade throughout the study period was calculated as $100 \times (T_c - T_1)/T_c$, where T_1 is the first twitch height in the train of four and T_c is the control twitch height as measured prior to administration of relaxant. Percent recovery was calculated as $100 \times T_1/T_c$.

Patients were assigned to one of three groups (n = nine per group). Endotracheal tubes were inserted in group 1 patients without the use of muscle relaxants. When control twitch height had been stable for 15 min, the patients in group 1 received an ED_{95} of doxacurium (0.024 mg/kg—a value previously determined at our institution). Patients in groups 2 and 3 received succinylcholine 1 mg/kg intravenously following induction of anesthesia; the trachea was intubated 1–2 min later. When the height of T_1 returned to 95% of T_c following succinylcholine, patients in group 2 received 0.024 mg/kg of doxicurium. Patients in group 3 received doxacurium (0.024 mg/kg) when T_1 returned to only 10% of T_c.

Patients were allowed to recover spontaneously from doxacurium-induced neuromuscular blockade whenever

* Clinical Research Fellow, Northwestern University.
† Clinical Professor of Anesthesia, Northwestern University.
‡ Professor of Anesthesia, Northwestern University.
§ Clinical Research Nurse, Northwestern University.
¶ Clinical Research Associate, Burroughs Wellcome Co.
** Clinical Research Scientist, Burroughs Wellcome Co.

Received from the Department of Anesthesia, Northwestern University, Chicago, Illinois; and Burroughs Wellcome Co., Research Triangle Park, North Carolina. Accepted for publication May 10, 1988. Supported by Burroughs Wellcome Co. Presented at the American Society of Anesthesiologists meeting in Atlanta, Georgia, 1987. Data collection and analysis were conducted at Northwestern University Medical Center.

Address reprint requests to Dr. Katz: 2101 Gradin Road, Apartment 709, Cincinnati, Ohio 45208.

Key words: Interactions. Neuromuscular relaxants: doxacurium; succinylcholine.

TABLE 1. Demographic Data

Group	Age (Years)	Sex (M/F)	Height (cm)	Weight (kg)
1	48 (17)	4/5	166 (10)	76 (11)
2	52 (16)	4/5	173 (11)	74 (12)
3	40 (14)	4/5	166 (11)	67 (18)

Results are mean ± (SD).

the duration of surgery permitted. At the completion of surgery, all patients who had a T_1/T_c ratio of less than 0.95 or a fourth twitch height in the train of four less than 75% of T_1 height received atropine and edrophonium as required for pharmacologic reversal. Ability to perform headlift for 5 s and a return of grip strength to preoperative status were assessed in all subjects 1 h after arrival into the recovery area and upon discharge to the wards.

Times to 90% and maximal blockade after doxacurium were measured in all patients. The intervals between doxacurium injection and recovery of T_1 height to 25% of control and between 25% and 75% recovery were also measured. Differences between the groups were examined using the Kruskal-Wallis test on an SPSS package; the null hypothesis was rejected at $P < 0.05$.

RESULTS

Results are expressed as mean ± SD. Demographic data were not significantly different between the groups (table 1). Table 2 lists the maximum blockade achieved, as well as onset and recovery data. Four patients in group 3 did not achieve 90% blockade following doxacurium. Complete ablation of twitch response occurred in two patients in group 1, one patient in group 2, and three patients in group 3. A significant decrease in maximum blockade achieved with doxacurium was shown in patients of group 3 compared to those of group 2. In terms of time to 25% recovery, the groups did not differ from each other. One patient in group 1, three in group 2, and one in group 3 did not achieve a spontaneous 75% recovery of T_1/T_c prior to completion of surgery, precluding measurement of recovery indices in these subjects. Group and individual subject data are shown graphically in figure 1.

TABLE 2. The Time Course of Neuromuscular Blockade with Doxacurium

Time to Maximum Block (Min)	Maximum Block (% Block)	Time to 90% Block (Min)	Time to 25% Recovery (Min)	RI (Min)
Group 1: Doxacurium given without succinylcholine				
10 (3)	97 (3)	6 (2)	55 (15)	51 (12) n = 8
Group 2: Doxacurium given at 95% recovery from succinylcholine				
10 (4)	98 (2)	5 (2)	81 (38)	43 (19) n = 6
Group 3: Doxacurium given at 10% recovery from succinylcholine				
9 (2)	90 (10)*	7 (2)†	43 (30)	44 (17) n = 8

Results are mean ± (SD). {n}, given if numbers <9. RI = interval from 25% to 75% recovery.
* Differs from group 2 only, $P < 0.05$.
† Only five patients reached 90% twitch depression.

In Group 2 patients, the interval from succinylcholine injection to 95% recovery from succinylcholine (and hence the interval between succinylcholine and doxacurium administration) was 12 ± 3 min. Time to 10% recovery from succinylcholine in group 3 was 7 ± 5 min. Duration of succinylcholine action in this study was similar to that reported in other studies.[10] As the onset time of doxacurium is slow relative to succinylcholine, all patients who received doxacurium following succinylcholine showed continuing but incomplete recovery, usually 30–40%, in the few minutes before onset of the nondepolarizing blockade.

At the end of surgery, edrophonium and atropine easily reversed residual neuromuscular blockade. The rate of recovery was inversely related to the degree of neuromuscular blockade present at the time of reversal. No adverse reactions to doxacurium were noted in this study.

DISCUSSION

Previous studies examining the neuromuscular effects of non-depolarizing relaxants following succinylcholine yielded conflicting data, possibly as a result of the different methodologies employed. For example, Katz demonstrated a potentiation of both duration and peak effect of pancuronium 0.02 mg/kg when given after complete recovery from succinylcholine 1 mg/kg during balanced anesthesia.[4] Walts and Rusin, on the other hand, found no change in duration of action of pancuronium when 0.05 mg/kg was given under similar conditions following succinylcholine.[5] Studies with vecuronium 0.04 mg/kg and 0.036 mg/kg given after full recovery from succinylcholine during balanced anesthesia also demonstrated an increase in effect and duration of action compared to administration without prior succinylcholine;[6,7] in the study of D'Hollander *et al.*, this increase was not influenced by the time interval (5–30 min) between the injections of succinylcholine and vecuronium.[6] Differences in outcome between these studies may be the result of the different dosages employed; the relative contribution of succinylcholine to neuromuscular blockade may become insignificant when non-depolarizing relaxant dosages are increased toward the ED_{95}. The pattern of potentiation appears true for atracurium as well; a study by Stirt *et al.*

using EMG monitoring showed that when atracurium 0.15 mg/kg was given after full recovery from succinylcholine, peak effect and duration were both increased.[11] Again, this may be the result of using a relatively small dose of atracurium, since 0.15 mg/kg of atracurium has been shown to produce only 66% depression of EMG activity.[11]

In clinical practice, administration of a non-depolarizing relaxant during the early part of recovery from succinylcholine blockade occurs frequently. However, few studies have examined the effects of partial succinylcholine blockade on subsequent non-depolarizing block, (in most studies, the non-depolarizing relaxants were given following complete recovery from succinylcholine). Walts and Dillon using d-tubocurarine 4 mg/m^2 body surface area following succinylcholine 40 mg/m^2 found significantly less blockade from the d-tubocurarine when it was given at 10% recovery from succinylcholine than when it was given alone.[9] However, the present study did not find a reduction of maximum effect when doxacurium was given at 10% recovery from succinylcholine compared to when it was given alone. Our study also demonstrated no change from control in the degree of neuromuscular blockade produced by doxacurium when given at 95% recovery from succinylcholine. Walts and Dillon additionally showed that d-tubocurarine at 8 mg/m^2 body surface area had no change in its duration of action (time to 10% recovery) whether administered alone, at 10% recovery, or at complete recovery from succinylcholine. This is similar to our finding of no difference in duration of doxacurium effect whether it was given alone or at 10% or 95% recovery from succinylcholine.

Waud suggested that succinylcholine antagonizes the competitive block of d-tubocurarine by producing a partial depolarization, raising the resting membrane potential closer to the threshold potential.[12] This condition might only be true in the situation where the non-depolarizing relaxant is given before recovery from the depolarizing agent, since several studies indicate no change or an increase in duration of effect when full recovery from succinylcholine is allowed prior to the non-depolarizer dose. Theories for succinylcholine-induced potentiation include the possibility that once depolarization block terminates, a number of end plate receptors are either still bound to succinylcholine or are unbound but left with an increased affinity for antagonists.[6]

In conclusion, the intensity of doxacurium-induced neuromuscular blockade is not significantly changed whether doxacurium is given during a deep succinylcholine block or when given following nearly complete recovery from succinylcholine. The duration of action of an ED_{95} of doxacurium administered alone does not differ from its duration of action following prior succinylcholine administration.

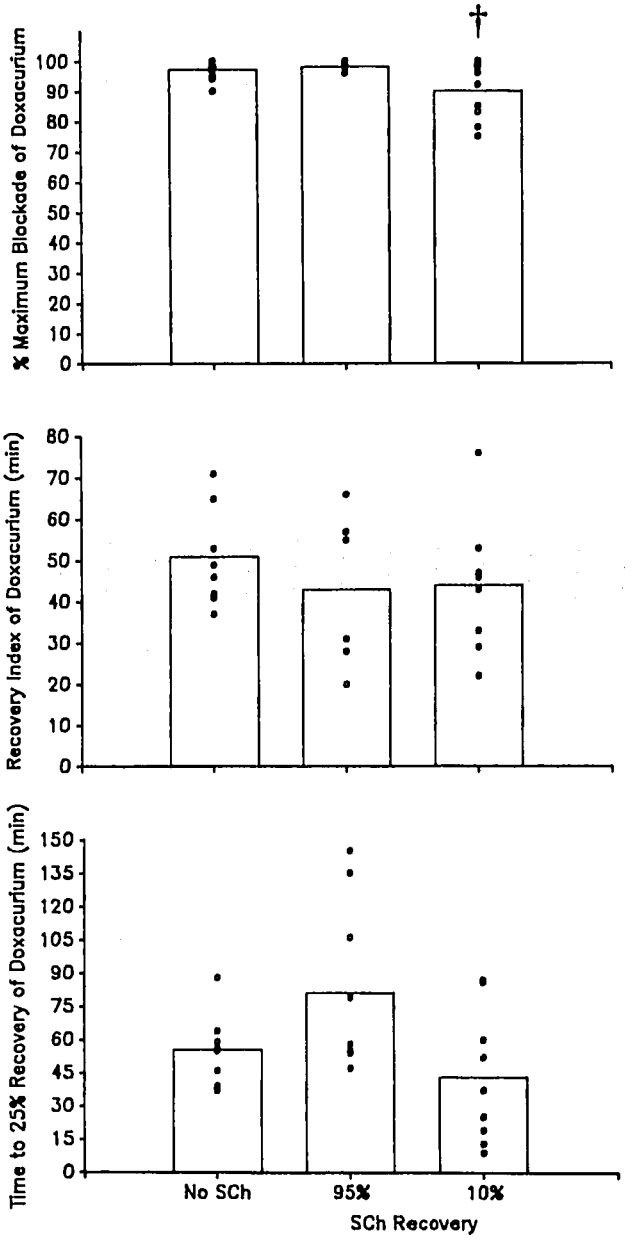

FIG. 1. Effects of succinylcholine on neuromuscular blockade of subsequently administered doxacurium. Circles = values for individual subjects; bars = mean values for each group; SCh = succinylcholine; recovery index = interval from 25 to 75% recovery; dagger = group 3 differs from group 2, $P < 0.05$ (Mann-Whitney).

REFERENCES

1. Mehta MP, Murray D, Forbes R, Choi WW, Gergis SD, Sokoll MD, Abou-Donia MM, Rudd GD: The neuromuscular pharmacology of BW A938U in anesthetized patients (abstract). ANESTHESIOLOGY 65:A280, 1986
2. Basta SJ, Savarese JJ, Ali HH, Sunder N, Bottros LH, Embree P, Schwartz A, Varin F, Rudd GD, Weakly JN: Neuromuscular and cardiovascular effects in patients of BW A938U: A new long-acting neuromuscular blocking agent (abstract). ANESTHESIOLOGY 65:A281, 1986

3. Larijani GE, Goldberg ME, Azad SS, Marr AT, Lessin JB, Hood LE, Ascher J, Rudd GD, Seltzer JL: The efficacy of doxacurium chloride for endotracheal intubation and provision of neuromuscular blockade in patients anesthetized with enflurane. Anesth Analg 67:S128, 1988
4. Katz RL: Modification of the action of pancuronium by succinylcholine and halothane. ANESTHESIOLOGY 35:602–606, 1971
5. Walts LF, Rusin WD: The influence of succinylcholine on the duration of pancuronium neuromuscular blockade. Anesth Analg 56:22–25, 1977
6. D'Hollander AA, Agoston S, DeVille A, Cuvelier F: Clinical and pharmacological actions of a bolus injection of suxamethonium: Two phenomena of distinct duration. Br J Anaesth 55:131–134, 1983
7. Krieg N, Hendrickx HL, Crul JF: Influence of suxamethonium on the potency of ORG NC 45 in anaesthetized patients. Br J Anaesth 53:259–261, 1981
8. Stirt JA, Murray AL, Katz RL, Schehl DC, Lee C: Atracurium during halothane anesthesia in humans. Anesth Analg 62:207–210, 1983
9. Walts LF, Dillon JB: Clinical studies of the interaction between d-tubocurarine and succinylcholine. ANESTHESIOLOGY 31:39–44, 1969
10. Walts LF, Dillon JB: Clinical studies on succinylcholine chloride. ANESTHESIOLOGY 28:372–376, 1967
11. Stirt JA, Katz RL, Murray AL, Schehland DL, Lee C: Modification of atracurium blockade by halothane and by suxamethonium. Br J Anaesth 55:71–75S, 1983
12. Waud DR: The nature of depolarization block. ANESTHESIOLOGY 29:1014–1024, 1968

Anesthesiology
69:607–608, 1988

Cimetidine and Succinylcholine: Potential Interaction and Effect on Neuromuscular Blockade in Man

JOSEPH A. STIRT, M.D.,* RICHARD J. SPERRY, M.D.,† COSMO A. DIFAZIO, M.D., PH.D.‡

Cimetidine, a histamine H_2 receptor antagonist, is often used as a premedication to increase gastric fluid *p*H. Cimetidine decreases liver blood flow[1] and inhibits microsomal drug metabolism.[2] In addition, *in vitro* inhibition of pseudocholinesterase activity by cimetidine has been demonstrated.[3] Since succinylcholine is metabolized by pseudocholinesterase formed in the liver, a potential exists for interaction between cimetidine and succinylcholine. Indeed, one recent study has demonstrated a markedly prolonged time to recovery of neuromuscular function after succinylcholine in patients receiving cimetidine *versus* controls during halothane anesthesia.[4] This prospective study was designed to determine the effect of cimetidine premedication on the onset and duration of succinylcholine-induced neuromuscular blockade in patients anesthetized with nitrous oxide and fentanyl.

* Associate Professor of Anesthesiology, University of Virginia Medical Center.

† Assistant Professor of Anesthesiology, University of Utah Health Science Center.

‡ Professor of Anesthesiology, University of Virginia Medical Center.

Received from the Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia; and the Department of Anesthesiology, University of Utah Health Science Center, Salt Lake City, Utah. Accepted for publication May 10, 1988.

Address reprint requests to Dr. Stirt: Department of Anesthesiology, Box 238, University of Virginia Medical Center, Charlottesville, Virginia 22908.

Key words: Antagonists: cimetidine. Interactions (drug). Neuromuscular relaxants: succinylcholine.

METHODS AND MATERIALS

This study was approved by the institution's Human Investigation Committee, and written informed consent was obtained from each patient. The subjects were 20 adult patients, ASA physical status 1 or 2, scheduled for elective surgery. The patients were randomly allocated into two groups of 10 each. Group 1 patients received cimetidine 400 mg p.o. at bedtime and 400 mg p.o. 90 min prior to induction of anesthesia. Group 2 patients acted as controls and did not receive cimetidine. No other premedication was given.

After placement of an arterial blood pressure cuff and EKG electrodes, anesthesia was induced with thiopental 4–6 mg/kg iv and maintained with fentanyl 3–5 μg/kg iv and N_2O, 67% in O_2. Succinylcholine 1 mg/kg iv was administered 3 min after thiopental.

Neuromuscular blockade was monitored with a force transducer (Grass FT-10) which measured adductor pollicus twitch tension in response to supramaximal ulnar nerve stimulation at 0.15 Hz, delivered for a duration of 0.15 ms *via* 25-gauge needles placed subcutaneously. A strip chart continuously recorded the force transducer measurements from 2 min before to 50 min after succinylcholine administration.

Times to initial twitch depression and to maximal neuromuscular blockade and the magnitude of neuromuscular block were measured, as were times to 10, 25, 50, 75, and 90% recovery of initial twitch tension. Student's *t* test was used to test statistical significance between groups, with $P < 0.05$ considered significant.