

Dose-response Relationships of Doxacurium Chloride in Humans during Anesthesia with Nitrous Oxide and Fentanyl, Enflurane, Isoflurane, or Halothane

Jeffrey A. Katz, M.D.,* Robert J. Fragen, M.D.,† Colin A. Shanks, M.D.,‡ Karen Dunn, R.N.,§
Barbara McNulty, M.S.,¶ G. David Rudd, M.S.¶

In a two-part study, the dose-response relationships of doxacurium chloride (BW A938U) were evaluated during general anesthesia maintained with commonly used anesthetic techniques. In part 1, cumulative dose-response methodology was used to establish the ED₉₅ of doxacurium in 36 patients receiving 70% nitrous oxide and fentanyl, or 50% nitrous oxide and either 1.26% enflurane, 0.84% isoflurane, or 0.57% halothane anesthesia. Mechanomyographic response to train-of-four stimulation was used to monitor neuromuscular blockade. The peak effect of doxacurium following each 5 µg/kg incremental dose was noted and a log-probit dose-response curve was constructed for each individual patient. The median ED₉₅s were 11 µg/kg, 6 µg/kg, 8 µg/kg, and 8 µg/kg for patients receiving fentanyl, enflurane, isoflurane, or halothane anesthesia, respectively. The median ED₉₅s were 24 µg/kg, 14 µg/kg, 16 µg/kg, and 19 µg/kg for patients receiving fentanyl, enflurane, isoflurane, and halothane anesthesia, respectively. In part 2, 72 additional patients received a rapid single injection of the ED₉₅ (n = 36) or 2 × ED₉₅ (n = 36) of doxacurium appropriate for the administered anesthetic as estimated from part one of the study. Peak effects of the ED₉₅ given as single injections correlated well with the results in part 1. There was a dose-dependent reduction in the time required to reach maximal blockade, and a corresponding increase in the duration of effect when twice the ED₉₅ was administered compared with that following the ED₉₅; mean onset times from injection to maximum block were 10–13 min for the ED₉₅s and 5–7 min for 2 × ED₉₅s, and mean times from injection to 25% recovery were 48–60 min for the ED₉₅s and 106–109 min for 2 × ED₉₅s. The anesthetic agent used did not result in significant differences between these mean times, but there was a significant difference when the two doses were compared for each anesthetic technique. The study results indicate that, when using the potent volatile agents, doses of doxacurium can be decreased 20–40% from doses required during anesthesia with nitrous oxide and fentanyl. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl. Anesthetics, volatile: enflurane; halothane; isoflurane. Neuromuscular relaxants: doxacurium. Pharmacology: drug interactions. Potency, anesthetic: ED₅₀; ED₉₅.)

DOXACURIUM CHLORIDE (BW A938U) is a new long-acting nondepolarizing skeletal muscle relaxant that has a benzylisoquinolinium structure similar to that of atracurium but a duration of action more closely resembling that of d-tubocurarine and pancuronium.^{1,2} Unlike most long-acting nondepolarizing relaxants in clinical use, doxacurium appears devoid of significant cardiovascular side effects.^{1–5}

Volatile anesthetics enhance the neuromuscular blockade produced by nondepolarizing relaxants. The extent of this enhancement varies with the relaxant studied and the volatile agent used. For example, the effect of pancuronium is enhanced more by isoflurane and enflurane than by halothane.^{6,7} Although isoflurane shifts the dose-response curve of pancuronium to the left approximately 50%, it shifts the dose-response curve of vecuronium and atracurium by only about 20%.⁸

In part 1 of this study, a cumulative dosing technique was used to determine the dose-response relationships of doxacurium in patients anesthetized with nitrous oxide and either fentanyl (balanced) or enflurane, isoflurane, or halothane. In part 2, single doses of the ED₉₅s determined from part 1 were given as rapid single injections to patients anesthetized with the four anesthetic techniques to assess the influence of the volatile agents on the onset and duration of doxacurium-induced blockade. Part 2 of the study also included assessment of onset of action and time for recovery following single doses of double the ED₉₅s during each anesthetic technique.

Materials and Methods

PART 1

Thirty-six patients, ASA physical status 1 or 2, were studied after they gave institutionally approved written informed consent. Patients were 19–69 yr of age, weighed 48–100 kg, and were scheduled for elective surgical procedures. Excluded were females of child-bearing potential; patients with clinical or biochemical evidence of cardiac, renal, hepatic, neuromuscular, or psychiatric disease; and patients who had been taking quinidine, lidocaine, trimethaphan, antihistamines, phenytoin, antidepressants, or aminoglycoside antibiotics prior to the study period. The majority of patients were premedicated with mor-

* Clinical Research Fellow, Northwestern University Medical School.

† Clinical Professor of Anesthesia, Northwestern University Medical School.

‡ Professor of Anesthesia, Northwestern University Medical School.

§ Clinical Research Nurse, Northwestern University Medical School.

¶ Clinical Research Scientist, Burroughs Wellcome Company.

Received from the Department of Anesthesia, Northwestern University Medical School, Chicago, Illinois; and the Burroughs Wellcome Company, Research Triangle Park, North Carolina. Accepted for publication October 31, 1988. Supported by Burroughs Wellcome Company, Research Triangle Park, North Carolina. Data collection and analysis conducted at Northwestern University Medical Center, Chicago, Illinois.

Address reprint requests to Dr. Fragen: Department of Anesthesia, Northwestern University, 303 East Chicago Avenue, Chicago, Illinois 60611.

phine and atropine approximately 90 min prior to the study period. Five patients, two in the halothane group, two in the enflurane group, and one in the isoflurane group, received no premedication. One patient in the enflurane group received midazolam because of an allergy to morphine.

For all patients, anesthesia was induced intravenously with thiopental, 2–5 mg/kg, and fentanyl, 2–12 µg/kg. Following induction, the trachea was sprayed with 4 cc of 4% lidocaine and intubated without the use of muscle relaxants. Patients were randomly assigned to receive a maintenance anesthetic (n = 9 in each anesthetic group) of 50% nitrous oxide and either 1.26% enflurane, 0.84% isoflurane, or 0.57% halothane to provide a total of 1.25 MAC. These are ¾ MAC concentrations using non-age-adjusted MAC values of 1.68%, 1.12%, and 0.76% for enflurane, isoflurane, and halothane, respectively.⁹ These end-expired concentrations were achieved before injection of doxacurium. An additional group was maintained with a balanced technique utilizing 67% nitrous oxide in oxygen with supplemental fentanyl, thiopental, and droperidol given as indicated for patient response to surgical stimulus. This response could be movement, autonomic responses, or elevations of blood pressure or heart rate 15% above control values. Ventilation was controlled to maintain the end-tidal P_{CO₂} between 32 and 38 mmHg. End-tidal concentrations of the inhalational agents and carbon dioxide were continuously monitored throughout the study period with mass spectrometry. Nasopharyngeal temperature was maintained above 35° C, chiefly by use of surface insulation.

The intensity of neuromuscular blockade was determined by measuring the force of thumb adduction in response to stimulation of the ulnar nerve at the wrist. A Grass S-44 nerve stimulator with a stimulus isolation unit delivered supramaximal square wave stimuli of 0.2 msec duration through surface electrodes in a train-of-four pattern (2 Hz over 2 s repeated every 12 s). Mechanomyographic response to stimulation was measured by a Devices ST-10 linear force transducer fixed to an armboard and attached to the thumb with a preload of about 300 g; responses were recorded on a Hewlett Packard® polygraph.

Percent neuromuscular blockade was calculated as $100 \times (T_c - T_1)/T_c$, where T₁ represented the height of the first twitch in the train-of-four, and T_c represented the control T₁ height as measured prior to administration of relaxant. Percent recovery was defined as $100 \times T_1/T_c$.

End-expired gas concentrations and measurements of neuromuscular function were allowed to stabilize for 15 min after intubation, whereupon doxacurium 5 µg/kg was given intravenously. Further incremental doses of 5 µg/kg each were administered when the T₁ height was

unchanged over three consecutive trains following the previous dose increment; additional doses were not given when at least a 95% depression of T₁ height occurred. Neuromuscular function was allowed to recover spontaneously whenever the duration of surgery permitted. At the termination of surgery, all patients who had a T₁ less than 95% of T_c or a fourth twitch height in the train-of-four (T₄) less than 75% of T₁ received atropine and edrophonium as required for antagonism of neuromuscular block. Adequate recovery and maintenance of neuromuscular function were clinically monitored by grip strength and head lift in the recovery area.

For each patient, data from doses producing between 1 and 99% neuromuscular blockade were transformed to a log-probit format and the dose-response relationship derived by linear regression. The ED₅, ED₅₀, and ED₉₅ were determined from the regression line for each patient, and analysis of covariance was performed on these values to evaluate intragroup parallelism and to provide intergroup comparisons. Criterion for rejection of the null hypothesis was $P < 0.05$.

PART 2

Experimental design of part 2 of the study was the same as part 1 until doxacurium was administered. In part 2, each of 72 patients (again randomly allocated to four anesthetic groups with n = 9 per group) received either the ED₉₅ or twice ED₉₅ of doxacurium appropriate for the anesthetic technique (as determined in part 1) as a rapid single injection over 5–10 s. No additional doxacurium was given. Neuromuscular blockade was allowed to recover as in part 1. The intervals between injection of doxacurium and 90% and maximum twitch depression were noted. Recovery between neuromuscular blockade was evaluated by noting the interval between injection to 25% recovery and the interval between 25% to 75% recovery (the recovery index). Maximum blockade produced in each patient receiving the ED₉₅ was evaluated to confirm that the ED₉₅s determined in part 1 were accurate. One-way analysis of variance was performed using an SPSS package to compare onset and recovery data between anesthetic groups and between dosage groups. Scheffe's test was used for *post hoc* comparisons. $P < 0.05$ was considered statistically significant.

Results

PART 1

The anesthetic groups were similar in terms of basic demographic data (table 1). Individual cumulative dose-response curves for all patients are illustrated in figure 1; table 2 lists the median ED₅₀s and ED₉₅s. All three groups anesthetized with the volatile agents differed significantly

TABLE 1. Demographic Data

Group	Age (years)	Weight (kg)	Height (cm)	Sex (M/F)
Part 1: Cumulative dosing				
Balanced	40 (13)	81 (14)	173 (7)	9/0
Enflurane*	37 (18)	74 (10)	168 (11)	6/3
Isoflurane	37 (13)	82 (10)	173 (9)	7/2
Halothane	41 (19)	78 (13)	180 (14)	8/1
Part 2: Single dose, ED ₉₅				
Balanced	48 (17)	76 (11)	166 (10)	4/5
Enflurane	35 (10)	78 (8)	172 (8)	8/1
Isoflurane	39 (11)	79 (7)	178 (5)	9/0
Halothane	51 (14)	72 (13)	171 (11)	6/3
Part 2: Single dose, two times ED ₉₅				
Balanced	49 (14)	79 (13)	168 (11)	5/4
Enflurane	48 (14)	72 (12)	163 (9)	4/4
Isoflurane	50 (15)	70 (15)	162 (9)	2/7
Halothane	46 (12)	81 (15)	172 (11)	5/4

Values for age, weight, and height are mean (SD).
* Patients receiving enflurane, isoflurane, or halothane were also breathing 50% nitrous oxide.

from the balanced anesthetic group in which no volatile agent was used. Differences in enhancement of neuromuscular block could not be demonstrated between any of the groups anesthetized with the volatile agents.

TABLE 2. Cumulative Dose-response Data for Doxacurium

Group	ED ₅₀ (mg/kg)	ED ₉₅ (mg/kg)
Balanced	0.0106†	0.0238†
Enflurane*	0.0064	0.0136
Isoflurane	0.0084	0.0163
Halothane	0.0083	0.0193

Results shown are median values for each anesthetic group.
* Patients receiving enflurane, isoflurane, or halothane were also breathing 50% nitrous oxide.
† Analysis of covariance demonstrated that the balanced anesthesia group differs from the volatile anesthetic groups ($P < 0.05$).

PART 2

Tables 3 and 4 show the onset and recovery data of doxacurium for part 2 of the study. One patient receiving enflurane was eliminated from the study, due to equipment failure during data collection. For the patients who received the ED₉₅ of doxacurium as a single injection, the mean maximum blockade produced in each group was found to be within one standard deviation of 95%. Although times to 90% blockade, maximum blockade, 25% recovery, and 75% recovery were not different between the four anesthetic groups for a given effective dose, dose-

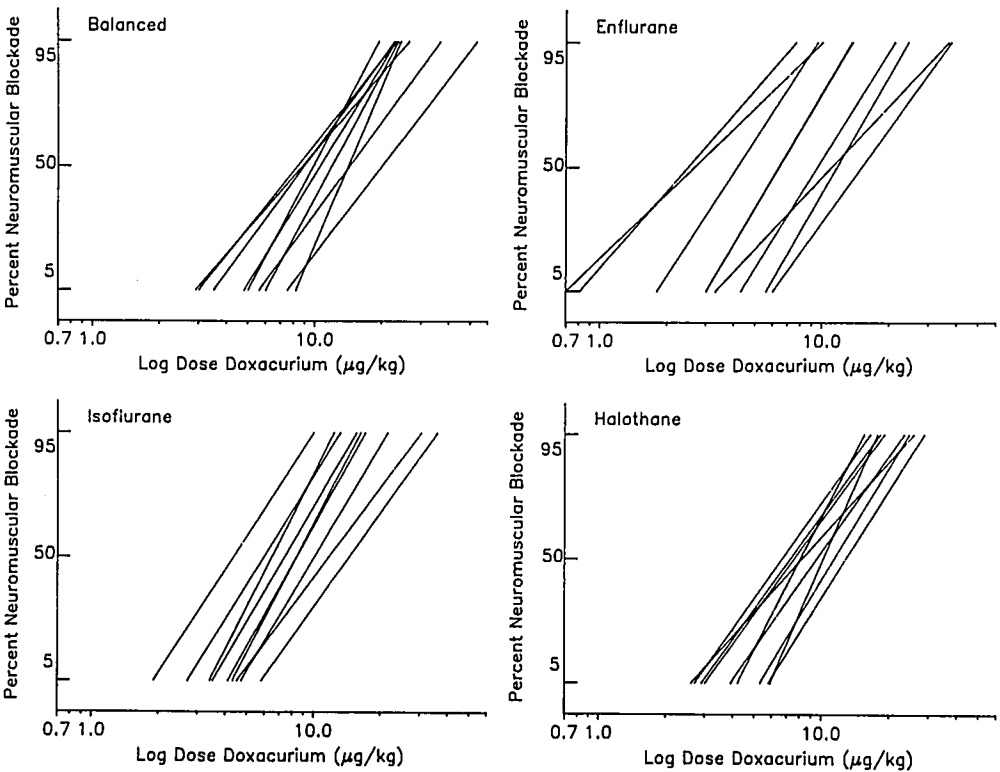


FIG. 1. Individual dose-response relations of doxacurium for each anesthetic group. Axes are in log dose-probit response format. Analysis of covariance showed that the curves for the enflurane group were shifted significantly to the left of those in the volatile agent groups. Particularly note the wide variability of response for the patients receiving enflurane.

TABLE 3. The Onset of Neuromuscular Blockade Induced by Single Bolus Administrations of the ED₉₅s and Twice ED₉₅s of Doxacurium

Balanced		Enflurane		Isoflurane		Halothane	
ED ₉₅	2 × ED ₉₅	ED ₉₅	2 × ED ₉₅	ED ₉₅	2 × ED ₉₅	ED ₉₅	2 × ED ₉₅
Maximal block (%)							
97 (3)	100 (1)*	92 (5)	99 (1)	93 (5)	99 (1)	94 (5)	100 (1)
Time to 90% block (min)							
6 (2)	3 (1)*	9 (3)	4 (1)	8 (2)	4 (1)	8 (3)	3 (1)
Time to maximal block (min)							
10 (3)	5 (2)*	13 (3)	7 (3)	12 (2)	7 (2)	13 (4)	6 (2)

Values are mean (SD).

* n = 8 for these groups. No significant differences were found

except between patients receiving the ED₉₅ and 2 × ED₉₅ within each anesthetic group.

dependent changes were demonstrated; those receiving twice the ED₉₅ of doxacurium differed from the corresponding anesthetic group receiving the single ED₉₅, with the greater dose being associated with faster onset and longer duration. Differences in regard to the 25–75% recovery index were not as consistent; doubling the dose did not significantly change the recovery index for either the halothane or enflurane groups.

Discussion

Because doxacurium was known to be a long-acting drug, a cumulative dose-response method would allow rapid comparison of potencies during various anesthetic regimens. Recognizing that the ED₉₅ is only one point on the upper portion of the sigmoid dose-response curve, the median ED₉₅s for single doses of doxacurium determined in part 1 of this study provided an average of 92–97% depression of the first response (table 1). The results also showed wide variability in the response to doxacurium, not unlike those found with other long-acting non-depolarizing relaxants.¹⁰ Although it appears that the variability was less with balanced or halothane anesthesia, it would take a much larger number of patients than that participating in this study to show whether this was a real difference.

The dose-response curve determined for doxacurium during balanced anesthesia was shifted to the left by 43% with enflurane, 31% by isoflurane, and 20% by halothane. The dose-response data for doxacurium in this study closely resemble the results of other work that used either single doses with multiple patients^{1,2} or cumulative dosing.¹¹ The ED₉₅ of doxacurium is reported between 23 and 26 µg/kg during balanced anesthesia.^{1,2,11} During anesthesia in adults receiving isoflurane or halothane, the ED₉₅s are between 14 and 19 µg/kg with no significant differences in the degree of enhancement.¹¹ There may be an age-related difference in the dose-response characteristics of doxacurium, because the mean ED₉₅s during halothane anesthesia in children are 27.3–29.3 µg/kg.^{12,13}

In this study, we did not age adjust our MAC values, but there was no difference in the ages of the patients receiving each anesthetic technique. Similar to our study, these other studies also administered the volatile agents for a limited time before doxacurium was given. It should be realized that the end-tidal concentrations of the volatile agents were more than the concentration achieved at the neuromuscular junction. If the volatile anesthetics were administered for a longer time or if a higher concentration of the volatile agents were administered, enhancement of doxacurium could have been different.

Onset and recovery data obtained in this study agree with results from other studies. Studies in which doxacurium, 23–30 µg/kg, was administered during balanced anesthesia reported an average time of 5–10 min to achieve 90% block,^{1,2,12–15} mean maximal blockade between 89 and 98%, and duration of surgically useful blockade (from injection of doxacurium to 25% recovery) of 60–90 min. Differences in the onset times between studies could be the result of the stimulation pattern used. This seems to be the case with atracurium, where a train-of-four stimulation, such as that used in this study, shortens the apparent onset time.¹⁶

Others have demonstrated the faster onset and increased duration of effect of doxacurium with increasing

TABLE 4. Recovery Data for Single Bolus Administrations of the ED₉₅s and Twice ED₉₅s of Doxacurium

		Balanced	Enflurane	Isoflurane	Halothane
Time to 25% recovery	ED ₉₅	55 (15)	48 (23)	54 (31)	60 (19)
	2 × ED ₉₅	107 (27) ^a	106 (36)	106 (37) ^d	109 (36) ^c
Time to 75% recovery	ED ₉₅	108 (18) ^c	116 (49) ^c	104 (62) ^c	124 (28) ^b
	2 × ED ₉₅	190 (69) ^a	152 (37) ^a	198 (80) ^c	164 (45) ^c
Recovery index	ED ₉₅	51 (12) ^c	75 (45) ^c	52 (29) ^c	63 (9) ^b
	2 × ED ₉₅	84 (44) ^c	74 (11) ^a	92 (41) ^c	69 (22) ^c

All data are mean (SD) and are reported in minutes.

For n < 9, ^a = 4, ^b = 5, ^c = 6, ^d = 7, ^e = 8. No significant differences were found except between patients receiving the ED₉₅ and 2 × ED₉₅ within each anesthetic group.

dosages.^{1,2,15,17,18} A dose of 50 $\mu\text{g}/\text{kg}$ produced 100% block in 4–8 min regardless of the type of anesthesia, while a dose of 80 $\mu\text{g}/\text{kg}$ required between 4 and 6 min to reach maximum effect.^{15,17,18} The time interval from injection to 25% recovery was 90–99 min following 50 $\mu\text{g}/\text{kg}$, and 169 to 210 min with 80 $\mu\text{g}/\text{kg}$.^{15,17}

In this study, the durations of action for each anesthetic technique were similar following the ED_{95} or $2 \times \text{ED}_{95}$. This implies that, for the same mg/kg dose, the duration of action of doxacurium would be prolonged with volatile anesthetic agents compared with the duration achieved with a nitrous oxide-narcotic anesthetic. The duration of action of doxacurium during balanced anesthesia is similar to that of pancuronium. Katz found that, with 1.5 times the ED_{95} of pancuronium (0.08 mg/kg), the time to 25% recovery was 86 min (range 43–133 min), and Mehta *et al.* found the time to 25% recovery at the same dose of pancuronium to be about 75 min.^{19,20} One and one-half of the ED_{95} of doxacurium during balanced anesthesia as determined in our study would be about 36 $\mu\text{g}/\text{kg}$; 40 $\mu\text{g}/\text{kg}$ was demonstrated by Mehta *et al.* to have a time to 25% recovery of 82 min and a time to 75% recovery of 97 min.

In summary, we determined the ED_{95} s of doxacurium during anesthesia with nitrous oxide and either fentanyl (balanced), enflurane, isoflurane, and halothane anesthesia using a cumulative dose-response technique. These were 24 $\mu\text{g}/\text{kg}$ for balanced anesthesia, and about one-third less in the presence of the volatile agents. Doxacurium was found to be an effective neuromuscular relaxant with pharmacodynamic properties resembling those of other long-acting nondepolarizing relaxants.

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 patient (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. Konstadt S, Thys DM, Reich D, Keusch D, Kaplan J: A study of the hemodynamic effects of BW A938U—A new long-acting nondepolarizing muscle relaxant (abstract). *ANESTHESIOLOGY* 67:A369, 1987
4. Stoops CM, Curtis CA, Kovach DA, McCammon R, Stoelting R, Warren T: Hemodynamic effects of BW A938U in coronary artery bypass graft and valve replacement patients receiving oxygen sufentanil anesthesia (abstract). *ANESTHESIOLOGY* 67:A368, 1987
5. Thys DM, Konstadt SN, Reich D, Hillel Z, Keusch D, Gettes M, Guffin A, Kaplan J, Mikula S, Marwin R: The effects of a new muscle relaxant, doxacurium, on left and right ventricular performance (abstract). *Anesth Analg* 67:S232, 1988
6. Miller RD, Way W, Dolan W, Stevens W, Eger E: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. *ANESTHESIOLOGY* 35:509–514, 1971
7. Linde HW, Dykes MM: Evaluation of a general anesthetic, isoflurane. *JAMA* 245:2335–2336, 1981
8. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey M, Sohn Y: Clinical pharmacology of vecuronium and atracurium. *ANESTHESIOLOGY* 61:444–453, 1984
9. Dripps RD, Eckenhoff JE, Vandam LD: Introduction to Anesthesia. Philadelphia, WB Saunders Company, 1988, p 108
10. Katz RL: Neuromuscular effects of d-tubocurarine, edrophonium, neostigmine in man. *ANESTHESIOLOGY* 28:327–336, 1967
11. Lynam DP, Caldwell JE, Miller RD: Isoflurane, halothane, and narcotic anesthetic dose-response for BW A938U (abstract). *ANESTHESIOLOGY* 67:A362, 1987
12. Sarnier JB, Brandom BW, Cook DR, Dong ML, Horn MC, Woelfel SK, Davis PJ, Rudd GD, Foster VJ, McNulty BS: Clinical pharmacology of doxacurium chloride (BW A938U) in children. *Anesth Analg* 67:303–306, 1988
13. Goudsouzian N, Alifimoff JK, Lin LM, Embree P, McNulty BF, Foster VJ: The dose response of BW A938U in children (abstract). *ANESTHESIOLOGY* 67:A366, 1987
14. Forbes RB, Mehta MP, Murray DJ, Choi WW, Sokoll MD, Gergis SD, Rudd GD, Krol T, Abou-Donia M, Cotten PJ: Effect of succinylcholine on subsequent neuromuscular blockade with BW A938U (abstract). *ANESTHESIOLOGY* 67:A363, 1987
15. Basta SJ, Debros F, Savarese JJ, Ali H, Embree P, Lai A, Schwartz A, DeAngelis R, Gallagher M, James N: BW A938U pharmacokinetics and dynamics in healthy surgical patients under isoflurane anesthesia (abstract). *Anesth Analg* 67:S9, 1988
16. Curran MJ, Donati F, Bevan DR: Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. *Br J Anaesth* 59:989–994, 1987
17. Glass PSA, Ginsberg B, Quill T, Shafron D, Ascher BS, Douglas C: Onset, duration, and reversal following doxacurium chloride (BW A938U) when combined with isoflurane. *Anesth Analg* 67:S73, 1988
18. 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
19. Mehta MP, Murray D, Forbes R, Choi W, Gergis S, Sokoll M, Abou-Donia M, Rudd G: The neuromuscular pharmacology of BW A938U in anesthetized patients (abstract). *ANESTHESIOLOGY* 65:A280, 1986
20. Katz RL: Clinical neuromuscular pharmacology of pancuronium. *ANESTHESIOLOGY* 34:550–556, 1971