

# The Neuromuscular Blocking and Cardiovascular Effects of Doxacurium Chloride in Patients Receiving Nitrous Oxide Narcotic Anesthesia

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The purpose of this study was to evaluate neuromuscular and cardiovascular effects of doxacurium chloride, a new long-acting neuromuscular blocking agent, during a stable state of nitrous oxide and narcotic anesthesia. Ninety-three ASA physical status I or II patients were studied after informed written consent had been obtained. Eighty-one patients (group A) received doxacurium. The 81 patients were divided into nine subgroups according to the dose of doxacurium administered (0.01–0.06 mg · kg<sup>-1</sup>). Patients in a control group (group B) (n = 12) received pancuronium. To assess neuromuscular responses, a force displacement transducer recorded the twitch response of the adductor pollicis muscle following ulnar nerve stimulation. The ED<sub>50</sub> and ED<sub>95</sub> for doxacurium were estimated to be 0.013 mg · kg<sup>-1</sup> and 0.023 mg · kg<sup>-1</sup>, respectively. The time to maximum twitch suppression following a dose of 1.0 (ED<sub>95</sub>) and 1.7 (ED<sub>95</sub>) was 10.3 ± 1.3 min and 7.6 ± 0.8 min, respectively. After an ED<sub>95</sub> dose of doxacurium the time to spontaneous recovery to 95% of control twitch height was 73.7 ± 8.7 min. With larger doses of doxacurium, 0.04 mg · kg<sup>-1</sup> (1.7 × ED<sub>95</sub>) and 0.05 mg · kg<sup>-1</sup> (2.2 × ED<sub>95</sub>), the time to spontaneous recovery to 95% of control twitch height was 125.8 ± 24.8 and 204.0 ± 21.2 minutes, respectively. When 25% twitch height recovery or more was present the reversal of doxacurium induced neuromuscular blockade was prompt. After administration of 0.04 mg · kg<sup>-1</sup> of doxacurium or 0.08 mg · kg<sup>-1</sup> of pancuronium, the time for spontaneous recovery to 25% of control twitch height recovery was 77.4 ± 7.5 min (n = 23) and 71.4 ± 6.7 min (n = 10), respectively. When identical multiple maintenance doses of doxacurium were administered, the subsequent neuromuscular block following each maintenance dose was of similar magnitude and duration. At 1, 2, and 5 min following pancuronium, heart rate and mean blood pressure increased. Following doxacurium small decreases in mean blood pressure occurred at 2 and 5 min, while heart rate decreased 5 min following drug injection. Doxacurium is a new, long-acting, nondepolarizing relaxant. Further study is warranted to assess the cardiovascular effects of this neuromuscular blocking drug in patients with cardiovascular disease. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl, morphine. Neuromuscular blocking drugs: doxacurium; pancuronium.)

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PROFILES for three hypothetical nondepolarizing relaxants were proposed by Savarese and Kitz in 1975.<sup>1</sup> These profiles were constructed with the aim of increasing the flexibility for muscle relaxant use and decreasing the side effects associated with the use of neuromuscular blocking drugs. Recent efforts in drug development have attempted to provide nondepolarizing muscle relaxants that meet these criteria and have either a short, intermediate, or long duration of neuromuscular blockade (NMB) and are in addition easily antagonized and free of cardiovascular or other untoward side effects.<sup>2</sup>

Atracurium and vecuronium met most of the goals outlined by Savarese and Kitz for neuromuscular blocking drugs with an intermediate duration of action.<sup>2</sup> Doxacurium chloride, a bis-quaternary ammonium compound with an ester linkage, is a nondepolarizing relaxant that in animal studies is long-acting and devoid of cardiovascular side effects.<sup>1</sup>

This study evaluated the neuromuscular and cardiovascular effects of doxacurium, a long-acting neuromuscular blocking agent, during nitrous oxide and narcotic anesthesia in healthy patients who required elective surgery.

## Materials and Methods

After approval of the protocol by the Human Research Committee, 93 ASA physical status I or II patients, age 18–59 years, who required elective surgery, were studied after written informed consent was obtained.

Patients were excluded from the study if they had a history of the following: 1) malignant hyperthermia; 2) unusual sensitivity to neuromuscular blocking agents; 3) alcohol or drug abuse; 4) clinically significant psychiatric, neurologic, cardiovascular, renal, or hepatic disease; or 5) exposure to aminoglycoside antibiotics, antihistamines, trimethaphan, quinidine, or lidocaine within 48 h of the study; or 6) asthma. In addition, patients were excluded if clinically significant ECG or laboratory abnormalities were detected by preoperative testing. Premedication included morphine (0.05–0.15 mg · kg<sup>-1</sup>, im) and atropine (0.004–0.008 mg · kg<sup>-1</sup>, im) or diazepam (0.1–0.2

<sup>1</sup> Savarese JJ, Wastila WB, Basta SJ, Beemer GH, Sunder N: Pharmacology of BW A938U (abstract). ANESTHESIOLOGY 59:A274, 1983.

mg · kg<sup>-1</sup>, po) 30–90 min prior to the induction of anesthesia. In the operating room lactated Ringer's solution in 5% dextrose was administered *via* an iv catheter. The ECG (Lead II) was continuously monitored throughout the treatment phase. The thumb of a restrained arm was attached to a force displacement transducer to measure and record the twitch response of the adductor pollicis muscle to ulnar nerve stimulation. The ulnar nerve was stimulated at the wrist using two 25-gauge subcutaneous needles. A Grass stimulator delivered square wave pulses at 0.15 Hz, 0.2 ms duration, and supramaximal voltage (20 V above maximum response). The elicited twitch response of the adductor pollicis produced by ulnar nerve stimulation, heart rate by ECG, and direct arterial pressure were continuously recorded on a four-channel recorder. Mass spectrometry (Perkin Elmer mass spectrometer) was used to measure end-tidal CO<sub>2</sub> levels and ventilation was controlled or assisted to maintain end-tidal CO<sub>2</sub> in a range of 30–42 mm. Temperature was maintained at 36.5 ± 0.5° C.

Anesthesia was induced with thiopental (3–4 mg · kg<sup>-1</sup>) and maintained with 60% N<sub>2</sub>O and 40% O<sub>2</sub>, and fentanyl (2–10 μg · kg<sup>-1</sup>) or morphine (0.10–0.20 mg · kg<sup>-1</sup>) and supplemental doses of thiopental. After establishing a baseline neuromuscular response (10–15 min following induction of anesthesia) a predetermined dose of doxacurium [group A (n = 81)] or pancuronium [group B (n = 12)] was injected intravenously over a 2- to 3-s period. Endotracheal intubation was not performed prior to or in the 10 min following doxacurium or pancuronium injection.

Group A consisted of 81 patients divided into nine subgroups (A1–A9) with nine patients in each subgroup. In group A the subgroups A1–A9 were assigned according to the dose of doxacurium administered during anesthesia (doses ranged from 0.010 to 0.060 mg · kg<sup>-1</sup>). The first four subgroups (A1–A4) were used to determine a dose–response curve for doxacurium. Subgroup A1 received an initial dose of 0.010 mg · kg<sup>-1</sup>. The dose administered to subgroup A2 was based on the average response of subgroup A1 and the assumption that the slope of the dose–response curve during nitrous oxide and narcotic anesthesia would be approximately the same as the slope of the neuromuscular response from the first human studies with doxacurium.\*\* Doses for subgroups A3 and A4 were estimated by regression analysis of the extrapolated dose–response curve for the completed patient subgroups in the study.

Subgroup A5, A6, and A7 all received the same dose of doxacurium (0.040 mg · kg<sup>-1</sup>). In subgroup A5 the time required for spontaneous recovery after a single 0.040 mg · kg<sup>-1</sup> dose was determined. In subgroup A6 sponta-

neous recovery was observed to 25% of control twitch height, and iv atropine 0.03 mg · kg<sup>-1</sup> and neostigmine 0.060 mg · kg<sup>-1</sup> were administered to determine the time required for recovery following pharmacologic reversal of neuromuscular block. In all other patients if there was residual block at the end of the surgical procedure as indicated by train-of-four ratio less than 0.75, iv atropine 1.2 mg and neostigmine 2.5 mg were used for reversal. In subgroup A7 eight of the nine patients received at least three supplemental doses of doxacurium (0.005 mg/kg<sup>-1</sup>) administered sequentially when twitch height recovered to 25% to determine the onset, magnitude, and duration of block that occurred following each supplemental dose. In subgroups A8 and A9 doxacurium bolus doses (0.050 and 0.060 mg · kg<sup>-1</sup>, respectively) were administered to determine the cardiovascular and neuromuscular effects of large drug doses.

In group B (n = 12) patients received pancuronium 0.080 mg · kg<sup>-1</sup> (1.5 × ED<sub>95</sub>)<sup>3</sup> but also received at least three successive supplemental doses of 0.010 mg · kg<sup>-1</sup> of pancuronium administered according to the paradigm described for subgroup A7.

The following neuromuscular variables were recorded in all patients: 1) time from injection to 90% and maximum neuromuscular block (four equally depressed twitch responses); 2) duration of maximum neuromuscular block (onset of maximal block to first evidence of recovery); and 3) time to 25%, 75%, and 95% recovery; and 4) time from 5–25% and 25–75% recovery of control twitch height (the recovery index). The initial twitch height prior to drug injection was used as the control twitch height. When twitch height recorded at full recovery differed by greater than 1 mm from the initial twitch height prior to drug injection, the twitch height at recovery was used to determine the time to 25%, 75%, and 95% twitch height recovery.

Blood pressure was monitored in subgroups A1–A3 by automated oscillometry or in subgroups A4–A9 and group B with an indwelling 20-gauge radial artery catheter. Cardiovascular data including heart rate and systolic, diastolic, and mean arterial pressure were collected and recorded every minute beginning 2 min prior to drug administration until 10 min following the injection of doxacurium or pancuronium. Blood samples for plasma histamine determination were obtained prior to and at 2 and 5 min following doxacurium administration in subgroups A4–A9. Plasma histamine levels were measured by radioenzymatic assay.<sup>4</sup> An additional blood sample was obtained from each patient for determination of serum cholinesterase activity and dibucaine number. Patients were evaluated in the recovery room at 30-min intervals until discharge to determine the continued adequacy of muscle strength as determined by adequate hand grip and sustained head lift.

\*\* Savarese JJ: Personal communication, 1983.

TABLE 1. Time in Minutes to 90% and Maximum NMB and 25% Recovery Following Doxacurium

Group	Doxacurium (mg · kg <sup>-1</sup> )	N	% Twitch Suppression	Time (min) to		
				90% Block	Maximum Block	25% Recovery*
A1	0.010	9	28.2 ± 4.9	—	16.0 ± 1.9	—
A2	0.015	9	61.9 ± 7.6	—	12.9 ± 1.5	23.0 ± 6.14 (n = 3)
A3	0.018	9	82.0 ± 5.0	—	11.5 ± 1.1	39.0 ± 1.35 (n = 6)
A4	0.023	7	92.4 ± 3.8	6.9 ± 0.9	10.3 ± 1.3	57.1 ± 12.8 (n = 6)
A5-A7	0.040	27	99.1 ± 0.3	4.1 ± 0.2	7.6 ± 0.8	77.4 ± 7.5 (n = 23)
A8	0.050	9	100.0 ± 0.0	3.4 ± 0.3	4.5 ± 0.5	124.8 ± 25.7 (n = 6)
A9	0.060	9	100.0 ± 0.0	3.1 ± 0.3	4.4 ± 0.3	122.8 ± 10.2

Results are expressed as mean ± SEM.

\* The time to 25% recovery is derived from the number of patients

who developed greater than 75% twitch height suppression and were observed to 25% twitch height recovery.

### STATISTICAL ANALYSIS

A doxacurium dose-response curve was constructed using the log-probit method of Litchfield and Wilcoxon<sup>5</sup> from the data obtained from subgroups A1-A4. Computerized analysis of the dose-response curve by least square linear regression yielded a straight line relationship.<sup>6</sup> Hemodynamic data were compared by two-way analysis of variance (ANOVA) to compare the changes prior to and following the drugs and between pancuronium and doxacurium. Two-way ANOVA was also used to compare the neuromuscular effects of repeated doses of pancuronium and doxacurium administered at 25% recovery. If an interaction existed, follow-up comparisons were performed. Bonferroni adjustment was used to protect the overall error rates. Significance was accepted at  $P < 0.05$ . Values are expressed as mean ± SEM.

### Results

Doxacurium produced a dose-dependent NMB (table 1). The ED<sub>50</sub> and ED<sub>95</sub> for doxacurium were 0.013 mg · kg<sup>-1</sup> and 0.023 mg · kg<sup>-1</sup>, respectively (fig. 1). Larger

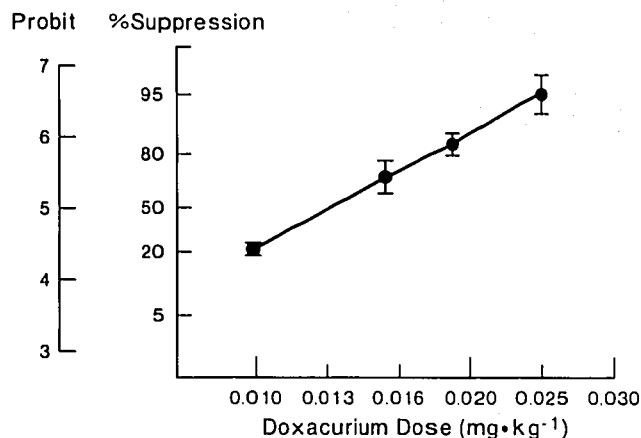


FIG. 1. Log probit dose-response for doxacurium during N<sub>2</sub>O narcotic anesthesia. Results are expressed as mean ± SEM.

doses of doxacurium decreased the time to onset of maximal block and increased the duration of NMB (fig. 2; table 1). Following 0.023 mg · kg<sup>-1</sup> of doxacurium, a dose anticipated to produce 95% twitch height depression (ED<sub>95</sub>), the time to maximum block was 10.3 ± 1.1 min with the time to spontaneous twitch height recovery of 73.7 ± 8.7 min (n = 3). In patients who received either 0.040 mg · kg<sup>-1</sup> of doxacurium or 0.080 mg · kg<sup>-1</sup> of pancuronium, the time to onset of maximum block was significantly longer in the patients who received doxacurium. The time to 25% twitch height recovery was similar with doxacurium and pancuronium [77.4 ± 7.5 min (n = 23) and 71.4 ± 6.7 min (n = 10) respectively] (table 2). The time for recovery from 5-25% twitch height was similar regardless of the initial dose [30.4 ± 8.1 (n = 4), 28.8 ± 2.5 (n = 21), 29.0 ± 2.5 (n = 5) minutes following 0.23, 0.40, and 0.50 mg · kg<sup>-1</sup> of doxacurium, respectively]. The time required for recovery from 25-75% of control twitch height was 32.3 ± 5.5 min (n = 3) and 41.6 ± 6.1 min (n = 5) following 0.023 mg · kg<sup>-1</sup> and 0.040 mg · kg<sup>-1</sup> of doxacurium, respectively. The time to 95% twitch height recovery following 0.040 mg · kg<sup>-1</sup> and 0.050 mg · kg<sup>-1</sup> doses of doxacurium was 125.8 ± 24.8 min (n = 3) and 204.0 ± 21.4 min (n = 4), respectively.

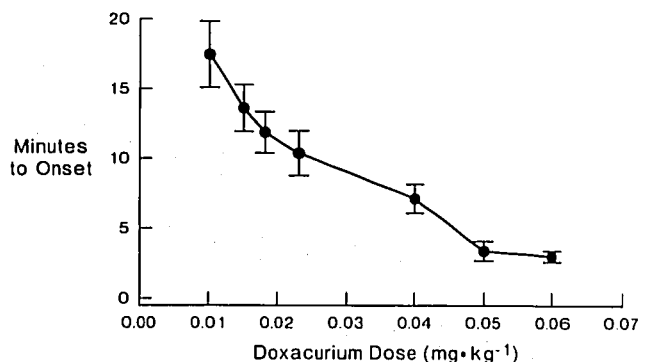


FIG. 2. Time to onset of maximum block with increasing doses of doxacurium. Results are expressed as mean ± SEM.

TABLE 2. Comparative NMB and Recovery Data for Approximately Equipotent Doses of Doxacurium and Pancuronium

	Dose	Time (min)			
		Onset to		Twitch Recovery	
		90% Block	Maximum Block	Begin Recovery	25% Recovery
Doxacurium (n = 27)	0.040	4.1 ± 0.2	7.6 ± 0.8	42.2 ± 4.8	77.4 ± 7.5
Pancuronium (n = 12)	0.080	2.3 ± 0.3*	5.1 ± 1.1*	42.2 ± 3.4	71.4 ± 6.7

Results are expressed as mean ± SEM.

\* Significantly different from doxacurium ( $P < 0.05$ ).

Following at least three successive supplemental doses of 0.005 mg · kg<sup>-1</sup> of doxacurium (subgroup A7) or 0.010 mg · kg<sup>-1</sup> of pancuronium (group B) administered at 25% twitch height recovery, the additional NMB produced, the time to maximal block and the time to 25% twitch recovery were similar for each supplemental dose of doxacurium or pancuronium (table 3). For an individual patient, the magnitude and duration of block produced by each of the three or more supplemental doses of doxacurium or pancuronium was similar.

In subgroup A6 when reversal of neuromuscular block was performed at similar twitch height recovery (26.3 ± 1.6% recovery) with atropine (0.030 mg · kg<sup>-1</sup>) and neostigmine (0.060 mg · kg<sup>-1</sup>), the time to 95% twitch height recovery was 4.8 ± 0.7 min. For other patients if neuromuscular recovery was not complete ( $T_4/T_1 < 0.75$ ), the NMB was reversed with atropine 1.2 mg and neostigmine 2.5 mg at the end of the surgical procedure. The mean percent block at the time of reversal was 48.2 ± 4.8 (n = 50) and the mean time to recovery of 95% twitch height was 4.3 ± 0.4 min. In one patient when reversal was attempted at less than 1% twitch height recovery, the time to 95% twitch height was delayed for 45 min. The twitch height recorded at the time of complete recovery for all study patients was 89 ± 4% of the initial twitch height recorded prior to drug administration.

The serum cholinesterase levels and dibucaine numbers were within normal limits in all patients who received doxacurium.

Doxacurium in a dose of 0.04 mg · kg<sup>-1</sup> decreased heart rate 5 min following injection and blood pressure at 2 min following injection while pancuronium in a dose of 0.08 mg · kg<sup>-1</sup> increased heart rate and mean blood pressure significantly 1 min following injection (table 4).

The mean histamine levels prior to doxacurium and at 2 min and 5 min following doxacurium in dose ranging from 0.23 to 0.60 mg · kg<sup>-1</sup> were 206 ± 154 pg · ml<sup>-1</sup>, 264.6 ± 218 pg · ml<sup>-1</sup>, and 239 ± 226 pg · ml<sup>-1</sup> respectively. In two patients plasma histamine levels increased from control levels by 200%, mean blood pressure and heart rate changes in these two patients were unchanged at 1 min and were 95% of pre-injection values at 2 and 5 min following doxacurium injection. The plasma histamine levels measured prior to and at 2 and 5 min following a doxacurium dose of 0.060 mg · kg<sup>-1</sup> (2.6 × ED<sub>95</sub>) were not significantly different.

### Discussion

The clinical neuromuscular characteristics of doxacurium are similar to other nondepolarizing neuromuscular blocking drugs. In this study, doxacurium produced a dose-dependent neuromuscular blockade. At any given dose, there was an expected variation in response between patients.<sup>7</sup> Larger doses of doxacurium decreased the time to onset of maximal blockade and increased the duration of relaxant effect. The duration of NMB from administration to 25% twitch height recovery (approximately 70

TABLE 3. Degree of Neuromuscular Block and Time to 25% Twitch Height Recovery Following Supplemental Doses of Doxacurium and Pancuronium Administered at 25% Twitch Height Recovery

	Dose (mg/kg)	Mean % Twitch Suppression at Time of Dose	Maximum % Twitch Suppression	Time to 25% Recovery (min)
Doxacurium				
1st maintenance	0.005	70.6 ± 1.3(9)	86.2 ± 1.4(9)	28.6 ± 5.4(8)
2nd maintenance	0.005	73.6 ± 2.1(9)	87.3 ± 1.7(9)	28.6 ± 9.4(8)
3rd maintenance	0.005	72.6 ± 1.5(9)	87.3 ± 1.4(9)	23.9 ± 3.7(7)
Pancuronium				
1st maintenance	0.010	73.8 ± 1.2(8)	91.8 ± 1.3(8)	25.3 ± 5.3(8)
2nd maintenance	0.010	73.6 ± 1.6(8)	89.6 ± 1.5(8)	25.4 ± 5.7(8)
3rd maintenance	0.010	71.7 ± 1.8(8)	89.4 ± 0.9(8)	22.4 ± 2.8(8)

Results are expressed as mean ± SEM; n values are given in parentheses.

TABLE 4. Heart Rate and Mean Blood Pressure Prior to and at 1 Min, 2 Min, and 5 Min Following Administration of Doxacurium and Pancuronium

	N	Predrug	1 Min	2 Min	5 Min
Heart rate					
Doxacurium	27	70.8 ± 2.5	68.7 ± 2.2	68.6 ± 2.9	63.3 ± 1.8*
Pancuronium	12	70.1 ± 4.7	76.1 ± 5.0*†	78.1 ± 5.2*†	81.6 ± 5.1*†
MBP					
Doxacurium	27	74.1 ± 2.3	72.7 ± 2.3	69.6 ± 2.0*	69.1 ± 2.0*
Pancuronium	12	73.7 ± 4.3	78.1 ± 4.0*†	78.2 ± 4.0*†	80.1 ± 3.8*†

\* Significantly different from predrug value ( $P < 0.05$ ).† Significantly different from doxacurium ( $P < 0.05$ ).

min) following a  $0.040 \text{ mg} \cdot \text{kg}^{-1}$  of doxacurium ( $1.7 \times \text{ED}_{95}$ ) was comparable to that of pancuronium  $0.080 \text{ mg} \cdot \text{kg}^{-1}$  ( $1.5 \times \text{ED}_{95}$ ).<sup>8</sup>

Failure of the twitch height to recover completely to its initial value is a problem inherent in the mechanomyogram. Assessment of the percent twitch height recovery assumes that an accurate control twitch height response is established prior to drug injection and that this control response is constant throughout the study period (*i.e.*, the twitch height response prior to drug injection and at full recovery should be equal). In this study twitch height at recovery ( $T_4/T_1 > 0.75$ ) was  $89 \pm 4\%$  of the predrug twitch height. This deterioration of the response may occur at any time throughout the study period. When the twitch response obtained at the end of the study period differed by greater than 1 mm from the initial twitch height measurement, we used this value to quantitate recovery and to assess the time to 25% and 75% recovery. In all other patients twitch height measured prior to drug injection was used as the control measurement throughout the study.

The onset of neuromuscular blockade was significantly faster with pancuronium than with doxacurium. Blood flow and diffusion of drug to the neuromuscular junction are important factors in the onset of NMB. Perhaps the difference in molecular structure of pancuronium and doxacurium is responsible for a faster NMB onset with pancuronium or, alternatively, the increases in MBP and HR and increases in cardiac output following pancuronium might hasten delivery of drug to the neuromuscular junction and speed the onset of NMB relative to doxacurium.

If cumulative relaxant effects were to occur with doxacurium, repeated doses administered at 25% recovery would produce progressively greater twitch suppression and also prolong recovery.<sup>3,9-11</sup> Supplemental doses of doxacurium administered at 25% recovery resulted in a similar degree and duration of NMB. In contrast to previous studies, repeated supplemental doses of pancuronium did not produce progressively greater twitch suppression or prolong recovery.<sup>3,10</sup>

Reversal of NMB was prompt following atropine and neostigmine when twitch height was 25% or greater; however, like other relaxants, in the one patient with less than 5% twitch height recovery present at the time of pharmacologic reversal of NMB, antagonism was delayed.<sup>12</sup> Further studies are warranted to evaluate antagonism of doxacurium in situations of more profound neuromuscular blockade (5–25% twitch height recovery).

The cardiovascular changes that occur with relaxants are usually related to autonomic effects<sup>13,14</sup> and/or to histamine release.<sup>15-17</sup> Statistically significant decreases in MBP occurred at 2 and 5 min following doxacurium, whereas decreases in HR occurred 5 min following doxacurium. The clinical signs of flushing, urticaria, and bronchospasm and the cardiovascular changes that are related to histamine release are usually associated with elevations in histamine of greater than 200% and coincide with peak blood levels of the drug. These increases in histamine would be anticipated to occur promptly after iv drug administration.<sup>15,16</sup> In two patients an increase in serum histamine level of greater than 200% did occur at 2 min or 5 min following drug injection, no concomitant changes in heart rate or blood pressure or other signs of histamine release were observed in either patient. Doxacurium was administered prior to endotracheal intubation and the start of elective surgery with blood pressure and pulse recorded each minute for 5 min (approximately 10–15 min following anesthesia induction). The significant decreases in MBP and HR following doxacurium may represent an undetermined cardiovascular effect of doxacurium, or the significant decreases may be related to the study design where BP and HR measurements were recorded for a 5-min period approximately 10–15 min following induction of anesthesia. A placebo group not included in this study would have provided additional comparative information about changes that occur unrelated to drug injection in MBP and HR in the 5-min period 10–15 min following anesthesia induction.<sup>18</sup> Similar to other studies, pancuronium resulted in significant increases in HR and MBP 1, 2, and 5 min following drug injection.<sup>13,14</sup>

Doxacurium, a nondepolarizing neuromuscular blocking agent with a duration of action similar to pancuronium, is approximately twice as potent as pancuronium. Decreases in blood pressure and heart rate occurred following doxacurium. These decreases were similar regardless of the size of the initial dose administered. There was no evidence of significant histamine release even following large iv bolus doses. When 25% or greater twitch height recovery was present, the neuromuscular blocking effect of doxacurium was readily antagonized with the commonly used doses of neostigmine. Additional studies are warranted to further assess the hemodynamic changes with doxacurium in healthy patients, as well as in patients with cardiovascular disease, and to establish the pharmacokinetics of this new, long-acting, nondepolarizing blocking drug.

### References

1. Savarese JJ, Kitz RJ: Does clinical anesthesia need new neuromuscular blocking agents. *ANESTHESIOLOGY* 42:236-239, 1975
2. Savarese JJ: The new neuromuscular blocking drugs are here. *ANESTHESIOLOGY* 55:1-3, 1981
3. Fahey MR, Sohn YJ, Cronelly R, Gencarelli P: Clinical pharmacology of Org NC45. *ANESTHESIOLOGY* 55:6-11, 1981
4. Beavan MA, Shaff RC: New inhibitors of histamine, N-methyl transferase. *Biochem Pharmacol* 28:183-189, 1979
5. Litchfield JT, Wilcoxon F: A simplified method evaluating dose effect experiments. *J Pharmacol Exp Ther* 96:99-113, 1949
6. Winer BJ: *Statistical Principle Design*, 2nd edition. New York, McGraw-Hill, 1971, pp 185-196, 301-305
7. Katz RL: Neuromuscular effects of d-tubocurare, edrophonium and neostigmine in man. *ANESTHESIOLOGY* 28:327-336, 1967
8. Katz RL: Clinical neuromuscular pharmacology of pancuronium. *ANESTHESIOLOGY* 34:550-558, 1971
9. Sokoll MD, Gergis SD, Mehta M, Ali N, Lineberry C: Safety and efficacy of atracurium (BW 33A) in surgical patients receiving balanced or isoflurane anesthesia. *ANESTHESIOLOGY* 58:450-455, 1983
10. Buzello W, Noldge G: Repetitive administration of pancuronium and vecuronium in patients undergoing long lasting operation. *Br J Anaesth* 54:1151-1157, 1982
11. Ali HH, Savarese JJ, Basta ST, Sunder N, Giofriddo M: Evaluation of cumulative properties of three new non-depolarizing neuromuscular blocking drugs BW A444U, atracurium and vecuronium. *Br J Anaesth* 55:107S-111S, 1983
12. Rupp SM, McChristian JW, Miller RD, Taboada JA, Cronelly R: Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium, or vecuronium. *ANESTHESIOLOGY* 64:711-717, 1986
13. Stoelting RK: The hemodynamic effects of pancuronium and d-tubocurarine in anesthetized patients. *ANESTHESIOLOGY* 39:645-657, 1973
14. Marshall RJ, Ojewole JAO: Comparison of the autonomic effects of some currently used neuromuscular blocking agents. *J Pharmacol* 66:77-78, 1979
15. Moss J, Rosow CE, Savarese JJ, Philbin DM, Knitten KJ: The role of histamine in the hypotensive action of d-tubocurarine in man. *ANESTHESIOLOGY* 55:19-25, 1981
16. Rosow CE, Basta SJ, Savarese JJ: BW785U: Correlation of cardiovascular effects with increases in plasma histamine. *ANESTHESIOLOGY* 54(suppl):270, 1980
17. Basta SJ, Savarese JJ, Ali HH, Moss J, Giofriddo M: Histamine releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. *Br J Anaesth* 55:1055-1065, 1983
18. Girard D, Sholman BJ, Thys DM: The safety and efficacy of esmolol during myocardial revascularization. *ANESTHESIOLOGY* 65:157-164, 1986