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# Clinical Pharmacology of Doxacurium Chloride

## A New Long-acting Nondepolarizing Muscle Relaxant

Salvatore J. Basta, M.D.,* John J. Savarese, M.D.,† Hassan H. Ali, M.D.,‡ Patricia B. Embree, C.R.N.A.,§
Ann F. Schwartz, C.R.N.A.,§ G. David Rudd, M.S.,¶ William B. Wastila, Ph.D.**

**Doxacurium chloride (BW A938U) is a bis-quaternary benzylisoquinolinium diester nondepolarizing neuromuscular blocking compound that is minimally hydrolyzed by human plasma cholinesterase. The effect of bolus doses of doxacurium ranging from 10 to 80 μg/kg were studied in 81 consenting ASA physical status I and II patients anesthetized with nitrous oxide-oxygen-fentanyl-thiopental. The neuromuscular and cardiovascular effects of doxacurium were compared with those of eight patients receiving 100 μg/kg of pancuronium receiving identical anesthesia. The calculated $ED_{95}$ for evoked twitch inhibition of the adductor pollicis at 0.15 Hz was 30 μg/kg. At 1.3 times the $ED_{95}$ dose of doxacurium, recovery times to 5% and 25% of control twitch height were 59.2 ± 4.1 (n = 23 of 26) and 75.7 ± 5.6 (n = 23 of 26) min respectively. For pancuronium comparable recovery times were 81.7 ± 10.3 (n = 8 of 8) and 83.0 ± 8.4 (n = 5 of 8) min. Residual doxacurium blockade was readily antagonized by neostigmine. No dose-related effect on heart rate or mean arterial pressure was seen with doxacurium at doses up to and including 2.7 times the $ED_{95}$ (80 μg/kg). Doxacurium administration did not result in any elevation of plasma histamine at doses up to and including 2.7 times the $ED_{95}$. In this study doxacurium appears to be a long-acting nondepolarizing relaxant with readily reversible neuromuscular blocking effects and devoid of cardiovascular effects. This profile offers clinical advantages over current long-acting agents and further clinical trials seem appropriate. (Key words: Antagonists: neuromuscular relaxants. Histamine. Neuromuscular relaxants: doxacurium chloride; BW A938U; Pancuronium.)**

A NEW COMPOUND, doxacurium chloride (BW A938U) (fig. 1), a bis-quaternary benzylisoquinolinium diester, has been shown in animals to be a long-acting nondepolarizing relaxant, without cumulative properties, readily antagonized by neostigmine and edrophonium, and with no autonomic effects or histamine release.[1],†† This report details efforts to determine the compound's potency, duration of action, cumulative properties, reversal by neostigmine, and effects on heart rate, blood pressure, and histamine release in humans.

### Methods

The study was approved by the Human Studies Committee of the Massachusetts General Hospital. Eight-nine healthy ASA physical status I and II patients about to undergo low-risk elective surgery gave written informed consent. Seventy-four men and 15 women without childbearing potential were included. Subjects ranged in age from 18 to 59 years and in weight from 52 to 100 kg, had no personal or family history of malignant hyperthermia, no known sensitivity to neuromuscular blocking agents, no allergies, and no major organ system disease; subjects were not receiving antibiotics or antihistamines prior to surgery.

On the day of study fasting subjects received oral diazepam (0.10 mg/kg) and intramuscular morphine (0.15 mg/kg) 1 h before induction of anesthesia. A large-bore venous cannula and, in certain groups, a 20-gauge radial arterial cannula were inserted percutaneously under local anesthesia. General anesthesia was then induced with iv thiopental (4–8 mg/kg) and fentanyl (6–8 μg/kg) in divided doses and maintained with nitrous oxide and oxygen in a semiclosed system (66%/33% inspired concentration) with additional thiopental and/or fentanyl as clinically required. In some patients receiving small doses of doxacurium, the trachea was sprayed with 4% lidocaine and intubation was performed before the relaxant was administered. In patients receiving the larger doses of doxacurium (30 μg/kg or greater), the trachea was intubated under doxacurium-induced neuromuscular blockade after the maximal cardiovascular and neuromuscular effects of the drug had been ascertained. Ventilation was controlled manually *via* a face mask or mechanically *via* the endo-

* Assistant Professor of Anaesthesia, Harvard Medical School at Massachusetts General Hospital.

† Professor of Anaesthesia, Harvard Medical School at Massachusetts General Hospital.

‡ Associate Professor of Anaesthesia, Harvard Medical School at Massachusetts General Hospital.

§ Clinical Research Coordinator, Department of Anaesthesia, Harvard Medical School at Massachusetts General Hospital.

¶ Project Leader, Anesthesia/Analgesia Section, Department of Clinical Neurosciences, Division of Clinical Research, Wellcome Research Laboratories, Burroughs Wellcome Co.

** Associate Director of Cardiovascular, Autonomic, and Biochemical Pharmacology, Wellcome Research Laboratories, Burroughs Wellcome Co.

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Address reprint requests to Dr. Basta: Department of Anaesthesia, Massachusetts General Hospital, 32 Fruit Street, Boston, MA 02114.

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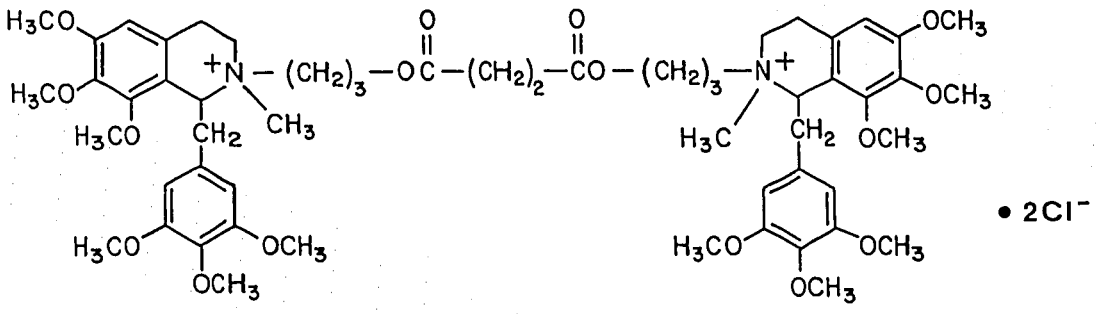


FIG. 1. Chemical formula of doxacurium chloride (BW A938U).

tracheal tube to maintain end-tidal $CO_2$ between 35 and 40 mmHg. Esophageal temperature was maintained between 35.0° C and 37.5° C.

In patients receiving smaller doses of doxacurium blood pressure was monitored every minute by oscillotonometry (DINAMAP®, Critikon, Jacksonville, FL), whereas in those receiving doxacurium doses at or above the estimated $ED_{95}$ (27 μg/kg from a prior trial in volunteers), direct arterial pressure was recorded with a Tektronix® transducer *via* the indwelling radial artery catheter. Lead II of the electrocardiogram was monitored continuously in all patients on an oscilloscope (Tektronix® model 412, Spacelabs, Irvine, CA) capable of generating a printout in the event of an abnormality. Heart rate was recorded continuously with a Grass 7P44 (Grass Medical Instruments, Quincey, MA) tachograph triggered by either the R-wave of the electrocardiogram or by the arterial pulse wave. All measurements were transcribed simultaneously on a Grass model 7 polygraph.

Neuromuscular function was monitored using the evoked mechanomyographic response of the ulnar nerve–adductor pollicis system. Responses were elicited by single supramaximal 0.2 ms square-wave stimuli generated by a Grass® S88 stimulator *via* an isolation unit and delivered at a frequency of 0.15 Hz through two 23-gauge steel needle electrodes placed subcutaneously over the ulnar nerve at the wrist. Force of thumb adduction was quantitated with a Grass® FT-10 transducer and a continuous polygraph recording was obtained.

In all cases doxacurium was injected as a rapid (5–10 s) bolus into the tubing of an iv infusion, following a 10–15 min period of stable blood pressure, heart rate, and twitch response. Measurements of maximum twitch depression, time to maximum depression, and changes in arterial pressure and heart rate were then made in the absence of stimulation due either to laryngoscopy or surgery.

Doxacurium was given to seven groups of patients who were studied sequentially according to an increasing dosage schedule. This method was chosen over a random dosage schedule because this was an early clinical trial and the authors elected to evaluate the cardiovascular stability of low doses before proceeding to higher doses. Because an individual's sensitivity to relaxants cannot be predicted and because the groups did not differ in age, sex, height, weight, or race, little bias should be expected using this protocol design. Doses ranged from 10 μg/kg (the approximated $ED_{25}$) to 80 μg/kg. Recovery of the twitch height to 5%, 25%, 75% and 95% of the initial twitch height control value was followed whenever possible. In those situations requiring additional relaxation during this initial recovery phase, neuromuscular blockade was reestablished using 5–15 μg/kg doxacurium as clinically required. In certain patients a fixed dose of 10 μg/kg was administered to reestablish blockade after 25% recovery from the initial bolus dose. Additional doses in this amount were given thereafter whenever twitch response recovered to approximately 25% of control height. This dose was chosen because it reinstituted deep blockade but did not abolish the twitch response entirely. In this initial and crude way any cumulative property of doxacurium could be evaluated by comparing the intervals between successive doses and by noting any lengthening of successive recovery times from 5–25% of control values and any increasing depth of block.

The dose–response curve for doxacurium was constructed by regression of probit values obtained from the percentage block achieved at doses of 10, 15, 20, and 30 μg/kg; the method was essentially that of Litchfield and Wilcoxon.[2] Zero twitch suppression was assigned a probit value of 2, and 100% suppression was assigned a probit value of 8. The dose of doxacurium administered to the initial study group was estimated from results of a previous trial in anesthetized human volunteers. Based on patient response to this dose, subsequent doses were chosen to provide adequate data for analysis.

To compare both the cardiovascular and neuromuscular effects of doxacurium with those of a standard agent,

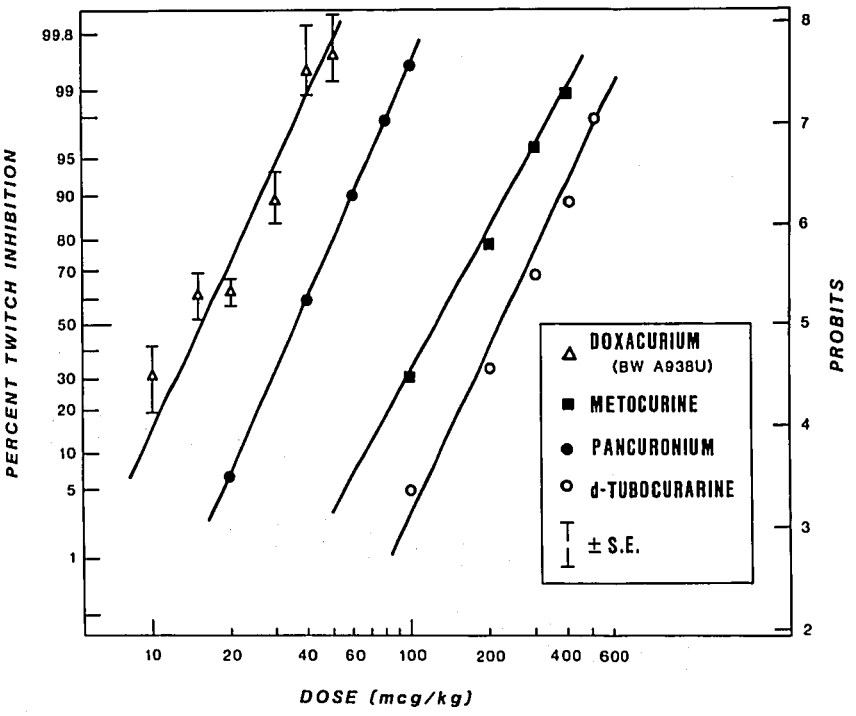


FIG. 2. Comparative dose-response curves for doxacurium, pancuronium, metocurine, and *d*Tc in patients under nitrous oxide-oxygen-narcotic-barbiturate anesthesia and evoked *via* single stimuli at 0.15 Hz. Data for pancuronium, metocurine, and *d*Tc are from Katz.[7]

a separate group of eight patients received an initial iv bolus dose of 100 μg/kg pancuronium. At 25% recovery of control twitch value a dose of 20 μg/kg was given to reestablish blockade; maintenance doses in this fixed amount were repeated whenever 25% twitch recovery was noted. Study conditions were identical to those for the patients receiving doxacurium.

When indicated, antagonism of residual doxacurium-induced block was performed by administering a mixture of neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg) as a 30–60 s iv bolus. The time from injection of the antagonist mixture to recovery of the twitch to 95% of control height was measured.

Venous or arterial samples of blood for determination of dibucaine number and plasma cholinesterase activity were drawn in all patients prior to induction of anesthesia. The method used for these determinations was that of Kalow and Genest.[3]

The rate of hydrolysis of doxacurium (relative to that of succinylcholine), as catalyzed by human plasma cholinesterase, was measured *in vitro* and calculated according to a modification of the method of Kitz *et al.*[4] Experiments were done at *p*H 7.4 and 37° C, using substrates at 5 μM concentrations. Determinations for substrate pairs were always done on the same day, using identical batches of enzyme. Typical enzyme activities were in the range of 20–40 μM acetylcholine hydrolyzed/ml/h.

Arterial samples of blood for measurement of plasma histamine were drawn immediately before administration of doxacurium and at 2 and 5 min after drug injection. Samples were drawn only from those patients scheduled to receive doses of 30, 40, 50, and 80 μg/kg (those at or above the $ED_{95}$). Histamine levels were assayed by a radioenzymatic technique previously described.[5] The sensitivity of the assay is 100 pg/ml and normal values are between 200 and 1,000 pg/ml. Variability of the assay is approximately 10%.

### STATISTICS

Appropriate comparisons were made by linear regression, Student's *t* test, and *F* test analysis of variance.[6] A *P* value of less than 0.05 was considered statistically significant. Testing for parallelism of the dose-response curves of doxacurium and other nondepolarizing relaxants was done by the method of Litchfield and Wilcoxon.[2]

## Results

### HYDROLYSIS IN VITRO

The hydrolysis rate *in vitro* as catalyzed by purified pooled human plasma cholinesterase was 0.16 ± 0.01 μM/h, or approximately 6% of the rate of succinylcholine.

### DOSE-RESPONSES AND DURATION

The dose-response curve for neuromuscular blockade was constructed using data from the 37 patients initially administered 10, 15, 20, and 30 μg/kg bolus doses of doxacurium. Ordinary least squares regression of the

TABLE 1. Maximal Twitch Suppression and Onset Times of Bolus Doses of Doxacurium (BW A938U) and Pancuronium

| Blocking Agent | Dose (μg/kg) | Maximum % Twitch Suppression | | | | | Minutes to Maximum Suppression | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Median | SE | Range | N | Mean | Median | SE |
| Doxacurium | 10 | 9 | 30.2 | 21.0 | 10.55 | (0–88) | 7 | 12.9 | 13.0 | 2.32 |
| | 15 | 9 | 61.1 | 68.0 | 8.82 | (13–93) | 9 | 13.2 | 13.0 | 1.09 |
| | 20 | 10 | 62.1 | 60.0 | 4.92 | (41–83) | 10 | 12.3 | 11.8 | 1.24 |
| | 30 | 9 | 89.1 | 97.5 | 4.73 | (67–100) | 9 | 10.2 | 10.5 | 1.27 |
| | 40 | 26 | 99.4 | 100.0 | 0.47 | (89–100) | 26 | 6.5* | 6.0 | 0.49 |
| | 50 | 9 | 99.6 | 100.0 | 0.44 | (96–100) | 9 | 5.9* | 5.0 | 1.13 |
| | 80 | 9 | 100.0 | 100.0 | 0.00 | (100–100) | 9 | 3.5† | 3.4 | 0.24 |
| Pancuronium | 100 | 8 | 99.9 | 100.0 | 0.13 | (99–100) | 8 | 2.4 | 2.3 | 0.21 |

* $P < 0.01$.

† $P < 0.05$.

probit of maximum twitch suppression on the common logarithm of the doxacurium dose yielded the regression line shown in figure 2. The probit scale is labeled with the percent twitch suppression and log dose is labeled as doxacurium dose in micrograms per kilograms. From the regression line estimates of the doxacurium $ED_{25}$, $ED_{50}$, $ED_{75}$, and $ED_{95}$ were found to be 11, 15, 20, and 30 μg/kg, respectively.

Patients receiving bolus doses of doxacurium at or below the $ED_{95}$ (10–30 μg/kg) exhibited a dose-related increase in mean twitch suppression from 30.2 ± 10.5 to 89.1 ± 4.7% blockade. At a bolus dose of doxacurium of 40 μg/kg (1.3 × $ED_{95}$), 23 of 26 patients had 100% twitch suppression. At 1.7 × the $ED_{95}$ (50 μg/kg), eight of nine patients had 100% twitch suppression, and at 2.7 × $ED_{95}$ (80μg/kg) all nine patients developed 100% twitch suppression. In patients receiving pancuronium at 100 μg/kg (1.4 × $ED_{95}$) seven of eight patients had 100% suppression (table 1).

The time to maximum blockade (onset time) was dose-related, being 10.2 ± 1.3 min at 30 μg/kg ($ED_{95}$) and decreasing to 3.5 ± 0.2 min at 80 μg/kg (2.7 × $ED_{95}$). In patients receiving pancuronium the mean onset time was 2.4 ± 0.2 min (table 1).

Times to 5% recovery following doxacurium bolus doses of 40, 50, and 80 μg/kg that produced 100% blockade were 58.1 ± 4.1 (23 of 26) 58.1 ± 8.1 (nine of nine) and 134.6 ± 22.7 (nine of nine) minutes (seven of nine), respectively. No differences in recovery times were found between the patients receiving 40 and 50 μg/kg whereas for those receiving 80 μg/kg the time to 5% recovery of twitch height was statistically significant from the other two groups.

The time to 5% recovery for patients receiving pancuronium group was 81.7 ± 10.3 (eight of eight) min (table 2).

Figure 3 plots the initial time course of early spontaneous recovery (start, 5%, and 25%) following the three largest doxacurium doses and following 100 μg/kg pancuronium as it includes almost all patients at these doses. The mean 5–25% spontaneous recovery times were 26.2 ± 1.5, 24.9 ± 2.3, and 33.8 ± 3.4 min for the 40 (n = 23), 50 (n = 9), and 80 (n = 7) μg/kg bolus doses of doxacurium. These values were not statistically different. The mean 5–25% spontaneous recovery time for the pancuronium patients was 18.6 ± 1.9 min (n = 5).

Twenty-two patients were given additional doses of doxacurium to supplement neuromuscular blockade at 20–25% recovery. The two patients receiving 5 μg/kg did not achieve sufficient supplemental relaxation. The three patients receiving 15 μg/kg had blockade of 100%. Seventeen patients received at least one additional dose of doxacurium of 10 μg/kg resulting in blockade between 90% and 98%. This dose yielded sufficient clinical relaxation and a measurable twitch response; it was chosen as the clinically effective maintenance dose for this study.

Seven patients receiving doxacurium received at least three maintenance doses following recovery to the 20–25% range (fig. 4). The time between such doses averaged 30–40 min. Although there is significant patient-to-patient variability, the neuromuscular and time course responses appear consistent for any given patient. Patient 68 appears to exhibit minor increases in depth of block and time intervals. However, supplemental doses were given based on preoperative weight despite the fact that there was an inflated tourniquet on the patient's left leg.

Sixty-seven of 81 patients receiving doxacurium and eight of nine receiving pancuronium received varying doses of neostigmine and atropine to antagonized residual neuromuscular blockade. Residual blockade was effectively antagonized in all patients. Thirty-six patients administered doxacurium received 60 μg/kg neostigmine at 5–90% spontaneous recovery. Times for antagonism of paralysis were 1.5–27.0 min (fig. 5; table 3).

Changes in mean arterial pressure, heart rate, and plasma histamine following doxacurium or pancuronium are shown in table 4. A statistically significant decrease in mean arterial pressure of 11% occurred following a

TABLE 2. Recovery Times Following A Single Bolus Dose of Doxacurium (BW A938U) and Pancuronium

| Blocking Agent | Dose (μg/kg) | Recovery Parameter (%) | N | Recovery Times (min)* | | |
|---|---|---|---|---|---|---|
| | | | | Mean | SE | Range |
| Doxacurium (BW A938U) | 10 | BR | 6 | 16.8 | 3.1 | 4.0–27.0 |
| | | 5 | 0 | — | — | — |
| | | 25 | 1 | 19.5 | — | — |
| | | 75 | 4 | 42.8 | 9.0 | 22.0–65.0 |
| | | 95 | 4 | 48.1 | 15.9 | 8.7–85.0 |
| | 15 | BR | 9 | 18.3 | 1.5 | 13.0–26.0 |
| | | 5 | 0 | — | — | — |
| | | 25 | 2 | 25.3 | 11.8 | 13.5–37.0 |
| | | 75 | 5 | 44.9 | 9.5 | 29.0–78.5 |
| | | 95 | 4 | 51.9 | 7.8 | 42.0–75.0 |
| | 20 | BR | 9 | 17.7 | 1.6 | 8.5–23.5 |
| | | 5 | 0 | — | — | — |
| | | 25 | 2 | 24.3 | 0.8 | 23.5–25.0 |
| | | 75 | 9 | 44.3 | 5.2 | 15.5–62.5 |
| | | 95 | 9 | 61.6 | 8.1 | 21.0–99.5 |
| | 30 ($ED_{95}$) | BR | 9 | 32.3 | 6.5 | 15.0–64.0 |
| | | 5 | 4 | 59.6 | 11.2 | 27.0–77.0 |
| | | 25 | 6 | 84.3 | 12.4 | 46.5–112.5 |
| | | 75 | 6 | 94.9 | 20.8 | 41.5–167.0 |
| | | 95 | 6 | 128.4 | 26.4 | 62.5–225.5 |
| | 40 (1.3 × $ED_{95}$) | BR | 26 | 45.4 | 3.9 | 11.0–87.0 |
| | | 5 | 23 | 59.2 | 4.1 | 19.5–110.0 |
| | | 25 | 23 | 77.5 | 5.6 | 20.2–122.5 |
| | | 75 | 7 | 126.0 | 20.7 | 52.5–185.0 |
| | | 95 | 5 | 118.8 | 22.9 | 63.5–177.0 |
| | 50 (1.7 × $ED_{95}$) | BR | 9 | 49.8 | 7.6 | 14.5–74.5 |
| | | 5 | 9 | 57.9 | 8.1 | 19.0–89.5 |
| | | 25 | 9 | 82.9 | 10.4 | 38.5–127.0 |
| | | 75 | 3 | 116.7 | 22.5 | 88.0–161.0 |
| | | 95 | 2 | 121.0 | 12.0 | 109.0–133.0 |
| | 80 (2.7 × $ED_{95}$) | BR | 9 | 124.7 | 21.5 | 67.0–275.0 |
| | | 5 | 9 | 134.6 | 22.7 | 74.0–285.0 |
| | | 25 | 7 | 158.0 | 30.4 | 109.5–337.5 |
| | | 75 | 3 | 185.2 | 10.0 | 167.0–201.5 |
| | | 95 | 2 | 219.3 | 15.8 | 203.5–235.0 |
| Pancuronium | 100 (1.4 × $ED_{95}$) | BR | 8 | 75.8 | 10.1 | 51.0–123.0 |
| | | 5 | 8 | 81.7 | 10.3 | 56.0–131.6 |
| | | 25 | 5 | 83.0 | 8.4 | 69.0–113.5 |
| | | 75 | 0 | — | — | — |
| | | 95 | 0 | — | — | — |

BR = beginning recovery; $ED_{95}$ = dose yielding 95% twitch suppression.

* From end of drug injection.

doxacurium bolus dose 20 μg/kg. No other groups receiving doxacurium (either lower or higher doses) exhibited any changes in mean arterial pressure. The group of patients administered pancuronium exhibited a statistically significant increase in mean arterial pressure of 17.7%.

Statistically significant decreases in heart rate occurred in the groups receiving doxacurium at 20 and 30 μg/kg (10.6% and 7.7%, respectively). Other groups receiving doxacurium did not exhibit any changes. A statistically significant increase in heart rate (13.8%) occurred in patients receiving pancuronium.

Blood samples for plasma histamine analysis were drawn at 0, 2, and 5 min from all patients receiving doxacurium bolus doses between 30 and 80 μg/kg. The broad range of values and standard errors within groups indicate the wide variability in plasma histamine concentrations among patients before and after doxacurium. However, using a doubling of the preinjection mean as a criterion, no increase in group plasma histamine occurred following

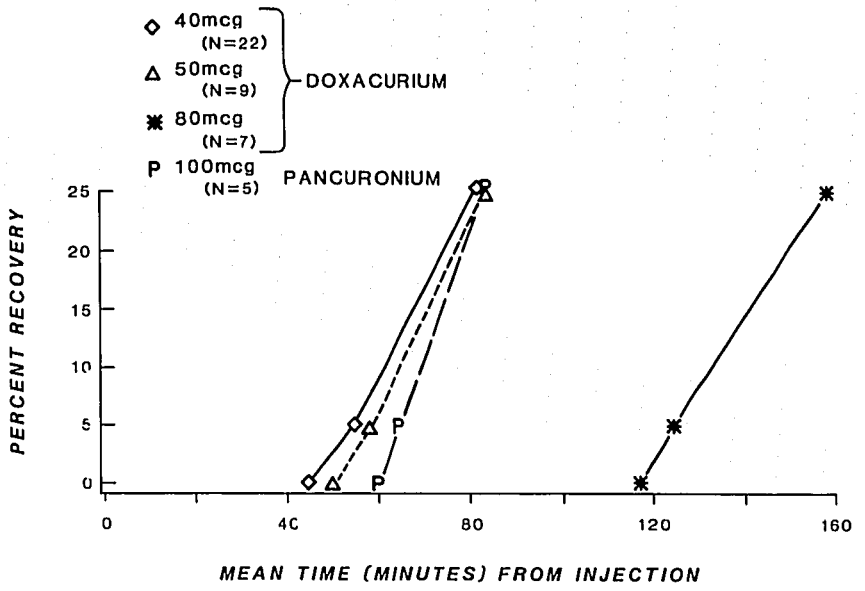


FIG. 3. Comparative mean spontaneous recovery curves of the single twitch to 5% and 25% of control following various bolus doses of doxacurium and 0.1 mg/kg of pancuronium. The mean 5–25% spontaneous recovery times were 26.2 ± 1.5, 24.9 ± 2.3, and 33.8 ± 3.4 min for the 40, 50, and 80 μg/kg doses of doxacurium. There was no statistically significant difference between groups. For pancuronium the mean 5–25% spontaneous recovery time was 18.6 ± 1.9 min.

doxacurium administration. No patient in the study exhibited redness over the vein into which doxacurium was injected, hives, flushing, or bronchospasm.

## Discussion

In this study of healthy patients undergoing elective surgery under $N_2O$-$O_2$-fentanyl anesthesia, doxacurium chloride has been shown to be an effective long-acting nondepolarizing muscle relaxant. At the estimated $ED_{95}$ of 30 μg/kg, doxacurium is 2–2.5 more potent than pancuronium, 9 times more potent than metocurine, and over 16 times more potent than *d*Tc.[7] Comparing the curves in figure 2 by the method of Litchfield and Wilcoxon[2] shows the respective dose–response curves to be parallel.

Comparing equipotent doses of doxacurium and pancuronium directly in this study, we found that time to maximum twitch depression was longer following doxacurium. At 40 and 50 μg/kg (1.3 and 1.7 × $ED_{95}$) the onset times for doxacurium were 6.5 ± 0.4 and 5.9 ± 1.1 min, respectively. This compares to a mean of 2.4 ± 0.2 min for 0.1 mg/kg pancuronium (1.4 × $ED_{95}$). In other studies under similar anesthetic conditions the mean onset time for metocurine (1.4 × $ED_{95}$) and pancuronium (1.4 × $ED_{95}$) was 4 min and for *d*Tc (1.2 × $ED_{95}$) was 5.7 min.[7] By increasing the dose of doxacurium to 80 μg/kg

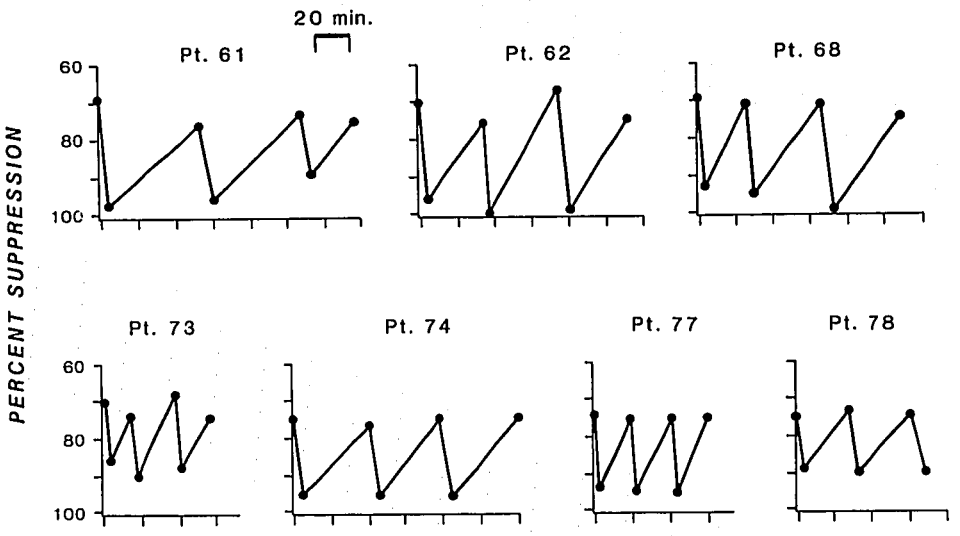


FIG. 4. These seven patients received at least three maintenance doses of 10 μg/kg of doxacurium between 20% and 25% spontaneous recovery. Although there is striking patient-to-patient variability, any one patient exhibits a consistent neuromuscular block and timing interval between doses.

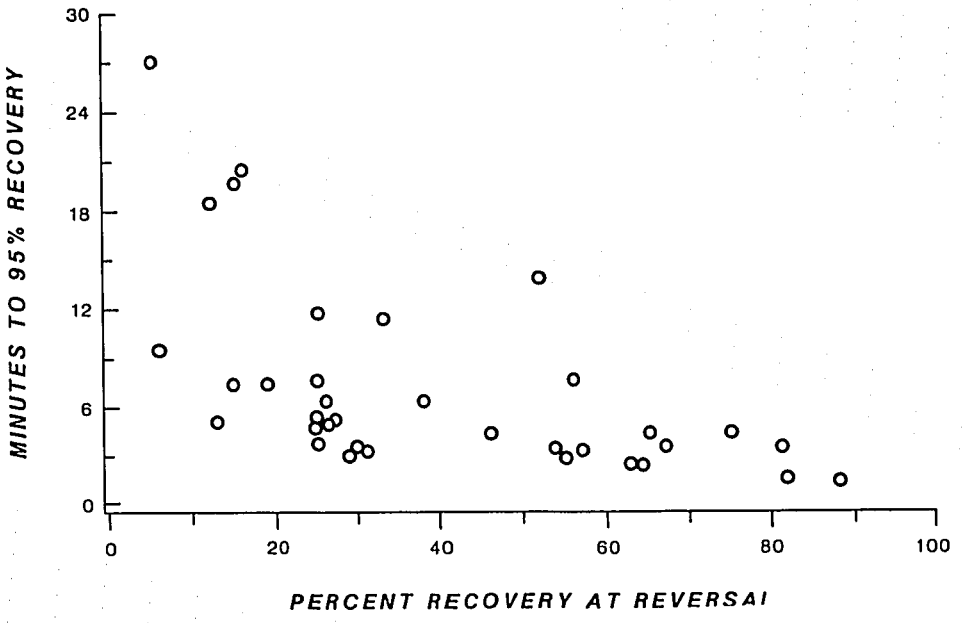


FIG. 5. Time course of antagonism of residual doxacurium-induced neuromuscular blockade with neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg). Each point represents a single individual. Similar to other nondepolarizing relaxants, the speed of reversal was inversely related to the depth of block.[7,8]

($2.7 \times ED_{95}$) the onset to maximum twitch suppression is reduced to 3.5 ± 0.24 min. Onset time becomes important when considering facilitation of tracheal intubation. Thus, doxacurium does not seem to be useful for rapid-sequence induction and tracheal intubation.

The first clinically important recovery time is that from injection to 5% recovery, a time at which anticholinesterase-induced reversal of residual paralysis might be accomplished. At 30 (six of nine patients), 40, and 50 μg/kg (1.0, 1.3, and $1.7 \times ED_{95}$) of doxacurium, the mean times to 5% recovery were 59.6 ± 11.2, 59.2 ± 4.1, and 57.9 ± 8.1 min, respectively. For the eight patients receiving pancuronium the mean time to 5% recovery was 81.7 ± 10.3 min.

The clinically effective duration of action (time from injection to 25% recovery) is a time interval after which a supplemental dose of relaxant might be needed or anticholinesterase-induced reversal should proceed rapidly. For doxacurium at 1.0, 1.3, and $1.7 \times ED_{95}$ these times are 84.3 ± 12.4, 77.5 ± 5.6, and 82.9 ± 10.4 min, respectively. The time to 25% recovery following pancuronium ($1.4 \times ED_{95}$) is similar at 83.0 ± 8.4 min but twitch recovered to 25% in only five of eight patients, whereas in 27 of 39 patients receiving doxacurium twitch recovered to this extent. Although the number of patients thus far studied is small, it might be suggested that at equipotent doses doxacurium has a similar duration of action to pancuronium. Furthermore, under similar anesthetic conditions Savarese *et al.* have shown 25% recovery times of 99 min for pancuronium ($1.4 \times ED_{95}$), 81 min for *d*Tc ($1.2 \times ED_{95}$), and 107 minutes for metocurine ($1.4 \times ED_{95}$).[7] Increasing the dose of doxacurium to 80 μg/kg ($2.7 \times ED_{95}$) extends the time to 25% recovery to approximately 160 min mostly at the expense of prolonging the duration of the period of 100% twitch depression. The mean 5–25% recovery times following 40, 50, and 80 μg/kg are 26.2 ± 1.5, 24.9 ± 2.3, and 33.8 ± 3.4 min respectively.

A close examination of the neuromuscular data following small doses of doxacurium and recovery times at all doses reveals marked variation about the mean. This variability is not unique to doxacurium. Although only one dose for pancuronium was evaluated in this study, recovery times differed by 100% among patients. This variation has also been shown by others. Savarese *et al.* have shown for a dose of metocurine of 0.2 mg/kg, a mean twitch suppression was about 80%, whereas the range was 17 to 99%.[7] In the same study at a metocurine dose of 0.3 mg/kg, a range of 42–167 min was seen for recovery to 25%. This same study showed recovery times of 48–108 min and 48–174 min for *d*Tc (0.6 mg/kg) and pancuronium (0.1 mg/kg). In addition, Katz demonstrated a mean twitch blockade of 88% with a range of 50–100% block with 40 μg/kg of pancuronium and recovery to 25% following 80 μg/kg of pancuronium of 86

TABLE 3. Reversal of Doxacurium (BW A938U)-Induced Neuromuscular Blackade with Neostigmine (0.06 mg/kg)

| Spontaneous Recovery at Time of Reversal | N | Time to 95% Recovery Following Reversal (min) | | |
|---|---|---|---|---|
| | | Mean | SE | Range |
| 5–24% | 8 | 14.4 | 2.8 | 5.2–27.0 |
| 25–90% | 28 | 5.1 | 0.6 | 1.5–14.0 |

Atropine (0.03 mg/kg) accompanied neostigmine.

TABLE 4. Maximum Changes in Heart Rate, Mean Arterial Pressure, and Plasma Histamine Following Doxacurium or Pancuronium

| Agent | Dose (μg/kg) | N | × $ED_{95}$ | Percent Control | | |
|---|---|---|---|---|---|---|
| | | | | HR | MAP | Histamine |
| Doxacurium (BW A938U) | 10 | 9 | — | 100.7 ± 4.0 | 101.9 ± 3.5 | NA |
| | 15 | 9 | — | 94.4 ± 2.5 | 95.2 ± 4.1 | NA |
| | 20 | 9 | — | 89.4 ± 2.5* | 89.0 ± 3.0* | NA |
| | 30 | 8 | 1 | 92.3 ± 2.6* | 95.3 ± 2.7 | 119.4 ± 20.5 |
| | 40 | 24 | 1.3 | 96.6 ± 1.6 | 99.8 ± 2.7 | 120.0 ± 18.0 |
| | 50 | 9 | 1.7 | 98.6 ± 2.1 | 99.9 ± 1.7 | 90.0 ± 19.3 |
| | 80 | 9 | 2.7 | 101.8 ± 2.2 | 98.5 ± 1.8 | 107.0 ± 19.3 |
| Pancuronium | 100 | 8 | 1.4 | 113.8 ± 2.1† | 117.7 ± 1.8† | NA |

Values are given as mean ± SE.
HR = heart rate; MAP = mean arterial pressure; NA = not assayed; × $ED_{95}$ = multiple of 95% blocking dose.
* $P < 0.05$.
† $P < 0.02$.

min with a range of 43–133 min.[8] This strengthens the notion that before administration of a drug to any particular patient, we have little prior knowledge of their individual pharmacokinetics and pharmacodynamics, thus reinforcing the strategy of giving small test doses of long-acting relaxants and assessing the effects before deciding on a clinically required dose. Those who prefer larger bolus doses of relaxant should note the following from this study. For doxacurium the median twitch suppression for 30 μg/kg is 97.5%. At higher doses it is 100%. The median recovery times to 5% and 25% at 40, 50, and 80 μg/kg of doxacurium are 48 and 58 min, 53 and 61 min, and 110 and 119 min, respectively.

During this study an appropriate maintenance dose for doxacurium upon recovery of the twitch to 25% was found to be 10 μg/kg. For those patients receiving three or more maintenance doses the mean percent depression of twitch height at the time of repeated doses was 72.8 ± 1.2%. The maintenance dose given at this point yielded a mean percent depression of 94.0 ± 0.9%. The average interval between maintenance doses was about 30 min with a range of 18–50 min. In any individual patient the degree of blockade and the timing increments between doses remained the same. With pancuronium at incremental doses of 20 μg/kg, only two patients received three or more repetitive doses. The average interval between doses was approximately 35 min.

Benzylisoquinolinium compounds, such as atracurium and the more distantly related compounds *d*Tc and metocurine, have a tendency to produce mild to moderate hemodynamic changes secondary to histamine release.[9] Doxacurium, although a benzylisoquinolinium ester, was not expected to exhibit this tendency. In cats at a dose of 0.64 ± 0.04 mg/kg no cardiovascular or autonomic effects were observed. The approximate $ED_{50}$ in cats for autonomic effects is 1.28 ± 0.06 mg/kg, giving an autonomic safety margin of 106. Further, Savarese *et al.*†† have shown no cardiovascular effects in rhesus monkeys or mongrel dogs at bolus doses up to 200 μg/kg.

In this study the 20 μg/kg dose of doxacurium produced approximately an 11% decrease in mean arterial pressure and heart rate. In the 30 μg/kg group an approximate decrease in heart rate of 8% was seen. No significant changes in mean arterial pressure or heart rate were seen in any other dosage groups below or above these two doses, and no significant increases in plasma histamine were noted for doses up to and including 80 μg/kg (2.7 × $ED_{95}$). Thus, doxacurium causes no dose-related effects on heart rate, blood pressure, or histamine release.

Stoops *et al.*[10] and Konstadt *et al.*[11] have studied doxacurium at doses up to 50 μg/kg in small groups of patients undergoing either CABG or valve replacements. Stoops *et al.*[10] observed no hemodynamic changes. Konstadt *et al.*[11] reported statistically significant mean decreases in heart rate (3 beats min), mean arterial pressure (8 mmHg), pulmonary artery pressure (3 mmHg), pulmonary capillary wedge pressure (3 mmHg), and central venous pressure (2 mmHg) and concluded that doxacurium had minimal hemodynamic effects in ASA physical status III and IV patients.

It is important to compare doxacurium with pipecuronium bromide, which is a bis-quaternary steroidal long-acting nondepolarizing muscle relaxant being used in eastern Europe and currently also undergoing clinical trials in the United States. During nitrous oxide-oxygen-fentanyl anesthesia and monitoring depression of the first twitch of the train-of-four, the $ED_{90}$ and $ED_{95}$ of pipecuronium were found to be 33.0 ± 1.6 μg/kg and 35.7 ± 1.5 μg/kg, respectively.[12,13] Thus, it would appear to be 30–40% more potent than pancuronium and slightly less potent than doxacurium. Caldwell *et al.* compared equipotent doses of pipecuronium (70 μg/kg) and pancuronium (100 μg/kg) during 0.7–0.8% end-tidal halothane.[14] The times to 25% recovery were 85 ± 19 min for pipecuronium and 119 ± 43 min for pancuronium. After doxacurium at 50 μg/kg (1.7 × $ED_{95}$) in this study during fentanyl anesthesia twitch height recovered to 25%

in 82.9 ± 10.4 min. Wierda *et al.* studied pipecuronium 200 μg/kg (4 × $ED_{90}$) in patients undergoing coronary artery bypass graft and found no hemodynamic changes.[15] It appears that in the few studies available, doxacurium and pipecuronium may be very similar in neuromuscular effects and hemodynamic stability.

In summary, doxacurium chloride was shown to be a potent long-acting nondepolarizing muscle relaxant. Doxacurium-induced neuromuscular blockade was readily antagonized using conventional anticholinesterase agents and doses. Doxacurium was devoid of dose-related effects on heart rate, mean arterial pressure, and histamine release at up to and including 2.7 × $ED_{95}$ for twitch suppression. This clinical profile may offer a useful alternative to the other long-acting neuromuscular blocking agents currently available, and, as such, doxacurium should undergo further clinical evaluation.

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