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Hemodynamic Effects of Doxacurium Chloride in Patients Receiving Oxygen Sufentanil Anesthesia for Coronary Artery Bypass Grafting or Valve Replacement

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Doxacurium chloride is an investigational long-acting neuromuscular blocking drug, which has been shown to be devoid of cardiovascular side effects when administered in modest doses to healthy patients. This is the first hemodynamic study of doxacurium in adult patients with cardiac disease. Forty-one patients scheduled to undergo cardiac surgery were studied. Anesthesia consisted of induction with midazolam 0.2–0.3 mg/kg and sufentanil 0.01–0.03 mg followed by an infusion of sufentanil at 0.03–0.06 mg · min^{-1}. Baseline hemodynamic data were collected during a stable state of sufentanil anesthesia. Doxacurium was then administered in doses of 1, 2, or 3 times its ED_{95} of 0.025 mg/kg. Hemodynamic measurements were repeated at 2, 5, and 10 min after doxacurium injection in the absence of surgical stimulation. An additional group of control patients received saline instead of doxacurium. Baseline hemodynamic measurements were similar among groups. There was a slight decrease in heart rate in all groups over time. However, there was no significant difference between the groups of patients receiving doxacurium and the control group in which the heart rate decreased progressively from 52 beats/min at baseline to 49 beats/min 10 min after doxacurium administration. At no time was there any significant change in mean arterial pressure, right atrial pressure, or cardiac output. Likewise derived hemodynamic variables including cardiac index, stroke volume, and pulmonary vascular resistance were unchanged. In addition to the decrease in heart rate, the hemodynamic changes, which reached statistical significance, were clinically insignificant and occurred predominantly in the group of patients receiving doxacurium 0.08 mg/kg. Baseline pulmonary artery occlusion pressure was 13 mmHg, and it increased to 14, 15, and 15 mmHg at 2, 5, and 10 min, respectively. Accordingly, pulmonary vascular resistance fell from 139 dyne · s · cm^{-5} at baseline to 114, 103, and 102 dyne · s · cm^{-5} at 2, 5, and 10 min, respectively. There was also a significant increase in stroke volume from 67 to 74 ml at 10 min in this group of patients receiving the largest dose. It is concluded that doxacurium has no clinically significant effect on measured or derived hemodynamic variables at doses up to 3 times its ED_{95}. This combination of a long duration of action and absence of circulatory effects makes doxacurium a potentially useful drug for patients with limited cardiac reserve undergoing prolonged operations. (Key words: Blood pressure: drug effects. Heart: cardiac output; rate; vascular pressures. Neuromuscular relaxants: doxacurium. Surgery: cardiac.)

DOXACURIUM CHLORIDE is an investigational nondepolarizing neuromuscular blocking drug. Its duration of action approximates that of pancuronium following equipotent doses.[1–3] The drug does not evoke the release of histamine and has been shown to be devoid of cardiovascular side effects at doses of 1.7 times its ED_{95} in healthy patients.[3] Animal studies have shown hemodynamic changes from control of less than 5% with doses 10–20 times the ED_{95}.** The purpose of this study was to assess the cardiovascular stability of doxacurium in adult patients undergoing coronary artery bypass grafting or valve replacement.

Materials and Methods

Forty-one patients 35 to 75 years of age scheduled to undergo coronary artery bypass grafting or valve replacement were enrolled in the study after obtaining an institutionally approved informed consent. All patients were ASA P.S. III or IV and met New York Heart Association criteria for functional Class I, II, or III. Patients were excluded from the study for any of the following reasons: childbearing potential; a history of chronic alcoholism and/or known drug abuse; evidence of clinically significant renal or hepatic impairment; recent exposure to antibiotics except penicillin, cephalosporins, or tetracyclines; exposure to H1- or H2-receptor blocking drugs within 48 h prior to anesthetic induction; exposure to antidepressants or phenytoin within 1 wk of entry into the study; exposure to iv vasoactive or cardiotonic drugs at the time of entry into the study.

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** Savarese JJ, Wastila WB, Basta SJ, Beemer GH, Sunder N: Pharmacology of BW A938U (Abstract). ANESTHESIOLOGY 59:A274, 1983.

TABLE 1. Study Groups

Group	n	Procedure	Drug	Dose
A	5	CABG	Doxacurium	0.025 mg/kg
B	9	CABG	Doxacurium	0.050 mg/kg
C	9	CABG	Doxacurium	0.080 mg/kg
D	9	CABG	Saline	0.080 ml/kg
E	7	VR*	Doxacurium	0.050 ml/kg
F	2	VR†	Doxacurium	0.080 ml/kg

CABG = coronary artery bypass graft.
* Aortic valve replacement (n = 4) or mitral valve replacement (n = 3)
† Aortic valve replacement (n = 2).

Preanesthetic medication administered 90 min prior to anticipated induction consisted of 10–15 mg morphine and 0.4 mg scopolamine intramuscularly along with 2–4 mg lorazepam orally. Beta-adrenergic blocking drugs, calcium entry blocking drugs, and oral or topical nitrates were continued as prescribed until the time of surgery. A peripheral iv infusion of Normosol® was established and a volume equal to the NPO deficit administered. The patients also received purified plasma protein fraction 500–1,000 ml. This pre-induction loading with colloid is a standard procedure at our institution to maintain preload and to facilitate the eventual removal of autologous blood after completion of the hemodynamic study. Initial monitoring included leads II and V5 of the ECG and direct radial arterial blood pressure, whereas a flow directed pulmonary artery catheter was inserted following induction of anesthesia. The ECG, arterial blood pressure, pulmonary artery, and right atrial pressures were recorded continuously using an Electronics for Medicine four-channel heat-sensitive paper recorder. The evoked electromyogram (EMG) of the adductor pollicis muscle following transcutaneous ulnar nerve stimulation at the wrist was recorded using the Datex® NMT monitor (Puritan-Bennett NMT 221). A train-of-four stimulus current at 2 Hz was delivered every 20 s.

Anesthetic induction was accomplished iv with midazolam 0.2–0.3 mg/kg and sufentanil 0.01–0.03 mg while the patient breathed 100% oxygen *via* face-mask. Tracheal intubation followed succinylcholine 1 mg/kg iv and topical lidocaine 160 mg. Anesthesia was maintained with an infusion of sufentanil 0.03–0.06 mg/min and controlled ventilation of the lungs to maintain end-tidal P_{CO_2} at 30–35 mmHg. Body temperature was monitored using a thermistor-equipped esophageal stethoscope.

During a period of stable vital signs at least 15 min after tracheal intubation in the absence of surgical stimulation and following complete recovery from the effects of succinylcholine as measured by EMG, baseline measurements were made of the following hemodynamic variables: mean arterial pressure (MAP), heart rate (HR), mean pulmonary artery pressure (MPAP), pulmonary artery occlusion pressure (PAOP), and right atrial pressure (RAP). Triplicate measurements of each variable were made and expressed as the mean value. Thermodilution cardiac output determinations were made and expressed as the mean of the values calculated from two well-formed curves using an American Edwards Laboratories Model COM-1 Cardiac Output Computer. Derived variables including cardiac index (CI), stroke volume (SV), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated using standard formulas after completion of the study.

There were six groups of patients (table 1). After baseline hemodynamic measurements three groups of the patients scheduled to undergo coronary artery bypass grafting received doxacurium 0.025 mg/kg (group A, n = 5), 0.050 mg/kg (group B, n = 9), or 0.080 mg/kg (group C, n = 9). These doses approximate 1, 2, and 3 times the ED_{95} of doxacurium. The control group consisted of patients with coronary artery disease who received normal saline 0.08 ml/kg (group D, n = 9). The patients with valvular heart disease were given doxacurium 0.050 mg/kg (group E, n = 7) or 0.080 mg/kg (group F, n = 2). In group E there were three patients who underwent mitral valve replacement and four patients who underwent aortic valve replacement. Both patients in group F underwent aortic valve replacement. All injections were made rapidly into a peripheral vein over 5–10 s. All measurements and calculations were repeated at 2, 5, and 10 min after injection with the patient supine. Bladder catheterization, shaving, and skin preparation were not permitted until all required hemodynamic data had been collected. Vasoactive and cardiotonic drugs were not administered during the study period.

The study was unblinded beginning with group A. Groups B and E were entered concurrently, as were groups C and F. Control group D was entered last, and these patients received doxacurium 0.050 mg/kg upon completion of the hemodynamic measurements to provide surgical relaxation. Any patient demonstrating 25% recovery of the first response to train-of-four stimulation during surgery was given an additional increment of doxacurium 0.025 mg/kg. Recovery from the neuromuscular block occurred spontaneously in the intensive care unit. After collection of all hemodynamic data anesthesia was maintained according to the individual needs of each patient.

Summary statistics were generated by treatment group for hemodynamic variables measured at baseline and 2, 5, and 10 min following injection of doxacurium

TABLE 2. Demographic Characteristics

		Groups A, B and C (n = 23)	Groups E and F (n = 9)	Group D (n = 9)	P value
Age (yr)	Mean	59	55	57	0.6395
	SD	8	14	7	
	Range	49–75	35–75	43–64	
Height (cm)	Mean	174	170	172	0.6237
	SD	11	12	10	
	Range	150–188	152–187	152–180	
Weight (kg)	Mean	84	82	93	0.2743
	SD	16	15	14	
	Range	58–119	61–104	69–114	
Body surface area (m^2)	Mean	1.99	1.93	2.05	0.4785
	SD	0.21	0.23	0.17	
	Range	1.53–2.41	1.62–2.29	1.83–2.30	
Sex	Female	5 (22%)	4 (44%)	1 (11%)	0.261
	Male	18 (78%)	5 (56%)	8 (89%)	
NYHA*	Class 1	2 (9%)	2 (22%)	0	0.541
	Class 2	6 (26%)	3 (33%)	4 (44%)	
	Class 3	15 (65%)	4 (45%)	5 (56%)	

* New York Heart Association criteria.

or saline. An ANOVA was performed to detect changes over time in hemodynamic variables for groups B, C, D, and E. When statistically significant changes were found by ANOVA, contrast tests, a general form of the paired *t* test, were performed to compare the hemodynamic variables at 2, 5, and 10 min after injection to baseline values. The continuous-type demographic data (age, weight, and body surface area) were analyzed using the Kruskal-Walis test, a nonparametric rank-sum procedure. The categorical demographic data (sex and New York Heart Association classification) were analyzed using a modified chi-square procedure.

Results

Demographic characteristics are summarized in table 2. There were no significant intergroup differences with respect to age, weight, body surface area, or New York Heart Association classification. Most of the patients undergoing coronary artery bypass graft procedures were male. Table 3 denotes the number of patients in each group receiving beta-adrenergic blocking drugs, calcium entry blocking drugs, and oral nitrates during the 12 h prior to beginning the study.

Hemodynamic data are presented in table 4. Pulmonary artery catheter data were incomplete for one patient in each of the groups B, C, and E. These three patients were not included in the analysis of MPAP and PAOP. Baseline hemodynamic measurements were similar among groups. There was a slight decrease in HR over time in all groups. There was an increase in MPAP from 23 mmHg at baseline to 24 mmHg at 10 min in group E. There was also a small but statistically significant rise in PAOP of 1–2 mmHg at 2, 5, and 10 min in group C. There was no significant change in any other hemodynamic variable over time.

Summary statistics for the derived hemodynamic variables are recorded in table 5. Incomplete pulmonary artery catheter data collection necessitated the exclusion of one patient each in groups B, C, and E. In group C SV increased from 67 ml at baseline to 74 ml at 10 min and PVR decreased from a baseline value of 139 dyne · s · cm^{-5} to 103 and 102 dyne · s · cm^{-5} at 5 and 10 min, respectively.

TABLE 3. Preoperative Vasoactive Drugs

	Group A (n = 5)	Group B (n = 9)	Group C (n = 9)	Group D (n = 9)	Group E (n = 7)	Group F (n = 2)
Beta-adrenergic blocking drugs	1	2	3	3	0	0
Calcium entry blocking drugs	4	7	5	5	0	0
Nitrates	2	5	3	7	0	0

TABLE 4. Measured Hemodynamic Variables (Mean ± SE)

	Group	n	Baseline	2 min	5 min	10 min
MAP (mmHg)	A	5	72 ± 5	67 ± 6	66 ± 5	74 ± 11
	B	9	70 ± 3	69 ± 3	68 ± 3	68 ± 3
	C	9	75 ± 3	76 ± 4	76 ± 3	76 ± 3
	D	9	74 ± 3	74 ± 3	74 ± 3	74 ± 3
	E	7	72 ± 4	72 ± 5	73 ± 5	74 ± 5
	F	2	65 ± 2	65 ± 2	67 ± 1	64 ± 1
HR (beats/min)	A	5	48 ± 2	47 ± 1	46 ± 2	47 ± 3
	B	9	55 ± 2	52 ± 2*	51 ± 2*	51 ± 2*
	C	9	54 ± 3	54 ± 3	54 ± 3	53 ± 3*
	D	9	52 ± 3	51 ± 3	50 ± 3*	49 ± 3*
	E	7	66 ± 7	63 ± 6*	62 ± 6*	61 ± 6*
	F	2	46 ± 1	44 ± 2	44 ± 1	45 ± 2
MPAP (mmHg)	A	5	20 ± 3	16 ± 3	19 ± 4	21 ± 4
	B	8	18 ± 2	18 ± 2	18 ± 2	18 ± 2
	C	8	19 ± 3	19 ± 3	20 ± 3	20 ± 3
	D	9	20 ± 2	20 ± 2	21 ± 1	21 ± 1
	E	6	23 ± 2	23 ± 2	23 ± 2	24 ± 3
	F	2	17 ± 3	18 ± 1	17 ± 2	18 ± 2
PAOP (mmHg)	A	5	16 ± 3	13 ± 3	15 ± 4	17 ± 5
	B	8	12 ± 1	13 ± 1	13 ± 1	14 ± 2
	C	8	13 ± 2	14 ± 3*	15 ± 3*	15 ± 3*
	D	9	15 ± 2	15 ± 2	16 ± 1	16 ± 1
	E	6	18 ± 2	18 ± 2	19 ± 2	20 ± 2
	F	2	13 ± 2	15 ± 3	15 ± 2	14 ± 2
RAP (mmHg)	A	5	12 ± 3	10 ± 3	11 ± 2	10 ± 2
	B	9	11 ± 1	10 ± 1	10 ± 1	10 ± 1
	C	9	12 ± 2	12 ± 2	13 ± 2	13 ± 2
	D	9	12 ± 1	13 ± 2	13 ± 1	12 ± 1
	E	7	10 ± 2	9 ± 2	10 ± 2	10 ± 2
	F	2	9 ± 2	10 ± 1	10 ± 1	10 ± 1
CO (l/min)	A	5	4.4 ± 0.4	4.3 ± 0.5	4.1 ± 0.3	4.4 ± 0.5
	B	9	4.1 ± 0.3	4.0 ± 0.4	4.0 ± 0.4	3.9 ± 0.3
	C	9	3.7 ± 0.3	3.6 ± 0.3	3.7 ± 0.4	3.8 ± 0.4
	D	9	3.9 ± 0.3	3.9 ± 0.3	3.8 ± 0.3	3.8 ± 0.2
	E	7	3.1 ± 0.2	3.1 ± 0.2	3.1 ± 0.3	3.2 ± 0.3
	F	2	2.9 ± 0.1	2.8 ± 0.2	2.8 ± 0.2	2.8 ± 0.1

* Different from baseline at the 0.05 level of significance.

Discussion

Rapid peripheral iv administration of doxacurium in doses that approximate 1, 2, and 3 times its ED_{95} did not cause clinically significant circulatory changes in adult patients undergoing elective coronary artery bypass graft or valve replacement operations while receiving oxygen sufentanil anesthesia. The absence of significant hemodynamic changes in cardiac patients is similar to data derived from patients without heart disease given doxacurium.[2,3]

This protocol was designed to minimize the effects of the anesthetic technique on the circulation. Histamine antagonists were avoided preoperatively. Intravenous vasoactive and cardiotonic drugs were not administered until all hemodynamic data had been collected. Prehydration with both colloid and crystalloid solutions increased preload and maintained CO and arterial blood pressure (BP) so that vasopressors were not required during the study period. A sufficient time interval was permitted before control measurements were obtained to allow HR and BP to return to normal following succinylcholine administration, laryngoscopy, and tracheal intubation. The patients were not stimulated in any additional way until all required data had been collected. Mechanical ventilation of the lungs was instituted in advance of all hemodynamic measurements. Sufentanil was chosen for its effect upon hemodynamic stability.[4] Anesthetic drug concentrations were established prior to injection of the study drug. It has been shown that background opiate anesthesia minimizes while potent inhaled drugs enhance the circulatory effects of muscle relaxants.[5–7]

The control group was an important part of this protocol to reveal any circulatory changes caused by the experimental design. For example, based on a study

TABLE 5. Derived Hemodynamic Variables (Mean ± SE)

	Group	n	Baseline	2 min	5 min	10 min
CI (l/min · m²)	A	5	2.1 ± 0.2	2.1 ± 0.2	2.0 ± 0.1	2.2 ± 0.2
	B	9	2.0 ± 0.1	2.0 ± 0.2	2.0 ± 0.2	1.9 ± 0.1
	C	9	1.9 ± 0.9	1.9 ± 0.1	1.9 ± 0.1	2.0 ± 0.1
	D	9	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
	E	7	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.2	1.6 ± 0.2
	F	2	1.6 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
SV (ml)	A	5	94 ± 10	91 ± 8	91 ± 4	93 ± 6
	B	9	75 ± 6	77 ± 6	77 ± 5	76 ± 5
	C	9	67 ± 8	69 ± 8	70 ± 8	74 ± 10*
	D	9	77 ± 4	78 ± 6	77 ± 6	78 ± 5
	E	7	50 ± 6	52 ± 6	53 ± 6	55 ± 7
	F	2	63 ± 3	63 ± 3	64 ± 7	63 ± 5
SVR (dyne · s · cm⁻⁵)	A	5	1,095 ± 121	1,050 ± 62	1,058 ± 76	1,133 ± 95
	B	9	1,223 ± 134	1,263 ± 155	1,253 ± 145	1,239 ± 114
	C	9	1,421 ± 118	1,459 ± 86	1,428 ± 112	1,411 ± 115
	D	9	1,315 ± 121	1,294 ± 102	1,334 ± 122	1,345 ± 107
	E	7	1,668 ± 139	1,670 ± 99	1,669 ± 142	1,653 ± 124
	F	2	1,543 ± 24	1,590 ± 36	1,624 ± 188	1,533 ± 124
PVR (dyne · s · cm⁻⁵)	A	5	84 ± 17	79 ± 23	84 ± 16	69 ± 12
	B	8	119 ± 15	97 ± 11	80 ± 14	79 ± 20
	C	8	139 ± 20	114 ± 18	103 ± 20*	102 ± 14*
	D	9	120 ± 20	100 ± 15	110 ± 15	100 ± 20
	E	6	112 ± 19	123 ± 21	107 ± 18	114 ± 12
	F	2	130 ± 42	87 ± 39	78 ± 26	105 ± 24

Different from baseline at the 0.05 level of significance.

with fentanyl it was hypothesized that HR slowing might occur while the data were collected during anesthesia with a sufentanil infusion in the absence of surgical stimulation.[8] This effect would be unrelated to doxacurium administration and could conceivably lower BP and CO. Such a decrease in HR was documented in both the control and experimental groups. Similarly, any hemodynamic changes resulting from mechanical ventilation of the lungs would be evident in the control group.

Plasma histamine concentrations have been shown to rise in some patients following doxacurium administration. The magnitude of the increase is small and is not associated with hemodynamic changes in healthy patients.†† To minimize the danger of even mild histamine-induced vasodilation in these patients with cardiac disease, doxacurium was injected peripherally. Central administration of drugs with histamine-releasing properties such as protamine has been associated with higher plasma histamine concentrations than peripheral administration.[9] Neither H1- nor H2-receptor blocking drugs were administered, perioperatively, however, so that histamine released by doxacurium might be reflected in circulatory changes. Prior administration of histamine antagonists has been shown to attenuate *d*-tubocurarine-induced hypotension.[10] Absence of significant hypotension and/or tachycardia following doxacurium suggests that histamine in clinically important amounts is not released.

All currently available long-acting neuromuscular blocking drugs produce significant cardiovascular side effects, which may be especially detrimental to patients with valvular heart disease or coronary artery disease. Rapid iv injection of the ED_{95} dose of *d*-tubocurarine may lower the BP 20% and variably increase HR secondary to histamine release.[11,12] Myocardial oxygen requirements increase while coronary perfusion pressure falls. Dangerous reductions in afterload may occur in patients with aortic stenosis. Similar changes occur with metocurine administration but are of less magnitude at clinically equivalent doses.[6,7] Pancuronium increases HR, BP, and CO by its vagolytic and sympathomimetic properties.[11,13] Myocardial ischemia may result from these autonomic effects.[14] Ventricular filling may be seriously impaired in patients with mitral stenosis. Gallamine also accelerates HR *via* an atropine-like effect and may adversely affect myocardial oxygen supply–demand relationships.[15]

The new intermediate-acting drugs produce minimal cardiovascular side effects. Atracurium in doses of twice its ED_{95} does not change HR, CI, MAP, or RAP and causes only a slight fall in SVR.[5] Vecuronium has even less effect on measured and calculated hemodynamic

†† Sokoll MD: Personal communication.

variables.[16] However, the pharmacokinetics of these two drugs dictate frequent dosing, the use of a continuous infusion, or the administration of very large bolus doses. Such techniques might be cumbersome and require frequent attention during prolonged cardiac operations when it may be necessary to simultaneously infuse several vasoactive, cardiotonic, and anesthetic drugs. Furthermore, hypothermia is associated with a prolonged duration of action of both atracurium‡‡ and vecuronium.[17] Therefore, proper drug doses are less predictable during cardiopulmonary bypass.

Traditional mechanisms by which nondepolarizing neuromuscular blocking drugs exert their hemodynamic effects are histamine release, ganglionic blockade, vagolytic, and sympathomimetic effects.[5-7,11-13,15] These effects occur within a 10-min period and tend to parallel the onset of neuromuscular block. Hemodynamic data collected over this period reflect changes due to these mechanisms. Therefore, an interval of 10 min for data collection is adequate to uncover any autonomic changes caused by doxacurium.

This study shows that doxacurium has no clinically significant effect on measured or calculated hemodynamic variables at doses up to 3 times its ED_{95}. The autonomic margin of safety seems as great for doxacurium as for vecuronium.[17] In addition, the duration of action is similar for doxacurium and pancuronium.[1] This combination of a long duration of action and absence of circulatory effects makes doxacurium a potentially useful drug for patients with coronary or valvular heart disease and limited cardiac reserve undergoing prolonged operations.

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