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The Cardiovascular Effects of Mivacurium Chloride (BW B1090U) in Patients Receiving Nitrous Oxide–Opiate–Barbiturate Anesthesia

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The dose–effect relationship of mivacurium chloride on arterial blood pressure, heart rate, and plasma histamine was determined in 97 consenting ASA physical status I–II patients receiving nitrous oxide–oxygen–opiate–barbiturate anesthesia. In the absence of surgical stimulation during steady state anesthetic conditions with controlled ventilation, average maximum change in tachograph-counted heart rate was 7% or less after 10–15-s injection of mivacurium at all doses from 0.03 to 0.30 mg/kg. Average peak change in mean arterial pressure measured *via* radial arterial catheter was 7% or less after all doses from 0.03 to 0.15 mg/kg. Transient (0.2–4.5 min) decreases in arterial blood pressure were noted after 10–15-s injection in some patients at 0.20, 0.25, and 0.30 mg/kg. When they occurred, these changes were usually accompanied by facial erythema lasting 2–5 min and were correlated with increases in plasma histamine level ($P < 0.001$). Facial erythema, decrease in blood pressure, and elevation of histamine level were all accentuated by increasing the dose of mivacurium and by more rapid injection of the drug. For example, mean blood pressure decreased an average of 13% after injection of mivacurium 0.25 mg/kg over 10–15 s. In contrast, during administration over 30 and 60 s of this dose, arterial pressure decreased 7.6 and 1.5%, respectively ($P < 0.001$, 10–15 s *vs.* 60-s injection). Average peak histamine level, which increased to 132% of control after administration of 0.25 mg/kg over 10–15 s, did not change after injection over 60 s. The cardiovascular response to mivacurium shows tachyphylaxis: the average decrease in mean blood pressure was significantly greater after first doses of 0.20 or 0.25 mg/kg (18 and 13%, respectively) than after identical second doses (2 and 8%). The authors conclude that the cardiovascular response to mivacurium in healthy patients is minimal at dosages up to and including 2 × ED_{95}. Blood pressure may decrease in some people after injection over 10–15 s of initial doses greater than 2 × ED_{95}. This response likely results from the release of histamine. The dose–ratio (ED_{50} for histamine-related events/ED_{95} for neuromuscular blockade) after rapid injection is 0.24/0.08 mg/kg, or 3.0. This safety ratio may be increased by slowing the rate of injection of mivacurium. (Key words: Anesthetics, gases: nitrous oxide. Neuromuscular relaxants, mivacurium: cardiovascular effects; plasma histamine.)

MIVACURIUM CHLORIDE (BW B1090U), hereafter referred to as mivacurium, is a new short-acting nondepolarizing neuromuscular blocking drug. The ED_{95} for neuromuscular blockade during nitrous oxide–opiate–barbiturate anesthesia is 0.08 mg/kg. The new drug is a bis-benzylisoquinolinium diester that is rapidly hydrolyzed by plasma cholinesterase.[1]

Benzylisoquinolinium compounds are known to share the generic side effect of a tendency to cause elevation of plasma histamine level together with associated phenomena such as facial erythema and transient decrease in arterial blood pressure.[2–6] §§ This well-known pattern suggested that, most likely, the cardiovascular effect of mivacurium should be qualitatively similar to that noted with other benzylisoquinolinium relaxants. Consequently, the purposes of the initial clinical trials described in this report were as follows: 1) to measure the dose–effect relationship of mivacurium on heart rate and mean arterial blood pressure with the use of continuous recordings in anticipation of dose-related decreases in blood pressure and possible increases in heart rate; 2) to correlate cardiovascular and/or cutaneous responses with any increases in plasma histamine levels; and 3) to determine the ED_{50} for clinically relevant elevation of plasma histamine and for two related phenomena—facial flushing and decrease in arterial pressure. The dose–ratio[2] (ED_{50} for histamine-

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related events/ED_{95} for neuromuscular blockade) in humans might then be calculated for mivacurium and compared with similar ratios for other relaxants such as atracurium, metocurine, *d*-tubocurarine, and doxacurium.

Methods

Patient Preparation

Ninety-seven ASA physical status I–II patients of either sex gave written informed consent to a protocol approved by the Subcommittee on Human Studies of the Massachusetts General Hospital. Subjects were 32.6 ± 1.0/9.7 (mean ± SE/SD) yr old (range, 18–49) and weighed 75.3 ± 1.2/11.7 kg (range, 50–100). They were free of neuromuscular, cardiovascular, hepatic, and renal disease and were not receiving medications known to affect neuromuscular or cardiovascular function. They received diazepam (0.1–0.2 mg/kg po) and morphine (0.1–0.15 mg/kg im) as premedication 1 h before arrival in the operating room.

Sixteen-gauge intravenous and 20-G radial arterial cannulae (the latter in patients who received mivacurium doses greater than ED_{95}) were inserted with the patient under local anesthesia before induction of general anesthesia. Additional morphine and/or diazepam were given iv as necessary to ensure adequate sedation. Anesthesia was then induced with thiopental (4–8 mg/kg) and fentanyl (4–8 μg/kg) iv in divided doses. The trachea was intubated either without a relaxant or after mivacurium-induced paralysis subsequent to the completion of all measurements (10 min after mivacurium injection). Nitrous oxide and oxygen (4 l/2 l) were given by controlled ventilation throughout the study period. End-tidal P_{CO_2} was maintained in the range 35–45 mmHg. Additional thiopental and/or fentanyl were given as necessary during induction and baseline measurements to minimize variation in blood pressure and heart rate. Esophageal temperature was kept between 34.5 and 37.5° C. Estimated fluid deficits were replaced with lactated Ringer's solution (1.5 $ml \cdot kg^{-1} \cdot h^{-1}$ of fasting) before administration of mivacurium.

During injection of mivacurium at ED_{95} and higher doses, direct arterial pressure and tachograph-counted heart rate were continuously recorded on a Grass® Model 7 Polygraph, together with adductor pollicis twitch evoked at 0.15 Hz, as described previously.[1] During administration of doses below ED_{95}, arterial pressure was measured at 1-min intervals by oscillotonometry (DINAMAP®). The electrocardiogram was monitored continuously on an oscilloscope (Tektronix® Model 412 or 414) with write-out capability in the event of need for documentation of possible rhythm disturbances.

Measurements

After a stable 10-min baseline period, during which blood pressure and heart rate varied less than 5%, mivacurium was injected over 10–15 s into a smoothly flowing iv stream. Cardiovascular responses were recorded for 10 min after injection or for a shorter period until blood pressure and heart rate had returned to within 95% of control levels. A maximum 10-min observation period was chosen because in initial studies in human volunteers any cardiovascular changes lasted much less than this (unpublished data). Measurements were completed in the absence of any surgical stimulation. Eight or nine people in eight dosage groups each received an initial bolus of mivacurium, 0.03–0.30 mg/kg, at the above injection rate.

After recovery of neuromuscular responses (twitch amplitude to >95% of control and train-of-four ratio to >70%), each patient received a second dose of mivacurium. In subjects who received initial doses of 0.20 or 0.25 mg/kg (2.5 and 3 × ED_{95}), over 10–15 s, the same dose was again given at the same rate, and cardiovascular measurements were again completed in the absence of surgical stimulation.

To test the influence of *slower* injection of initial doses of mivacurium on cardiovascular responses at dosage above 2 × ED_{95}, injection of 0.20 or 0.25 mg/kg was done over 30 or 60 s to three additional groups of nine patients (table 1).

Plasma Histamine Concentration

Plasma histamine level was assayed after all doses larger than the ED_{95} (dose range, 0.10–0.30 mg/kg). Arterial blood samples were taken immediately before and at 2 and 5 min after mivacurium injection. Samples were immediately heparinized, centrifuged under refrigeration, and stored at −70° C in polypropylene tubes for later analysis. Samples were analyzed according to a refinement[7] of the radioenzymatic method originally described by Moss *et al.*[8]

Histamine was converted to its tritiated methyl derivative with the use of S-(^{3}H) adenosyl methionine as the methyl donor and histamine N-methyl transferase from rat kidney as the enzymatic catalyst. Samples were analyzed in duplicate. The sensitivity of the assay is 100 pg/ml, and normal values are between 200 and 1,000 pg/ml. The assay is linear over a wide range. Variability of the assay is approximately 10%.[7,8]

Calculation of Dose Ratios: ED_{50} for Histamine-related Events/ED_{95} for Neuromuscular Blockade

An ED_{50} for histamine-related events was obtained in three ways: first, as the dose causing facial erythema in

TABLE 1. Mean Arterial Pressure (MAP) and Heart Rate (HR): Maximum Deviation from Baseline during the First 10 Minutes after Various First-bolus Doses of Mivacurium*

Dose (mg/kg)	Duration of Injection (s)	n	MAP (mmHg) Baseline	MAP (mmHg) Peak Effect†	Percentage of Baseline	HR (beats/min) Baseline	HR (beats/min) Peak Effect†	Percentage of Baseline
0.03	10–15	9	72 ± 2 (63–80)	71 ± 3 (65–83)	100 ± 3 (93–115)	58 ± 3 (47–70)	55 ± 2 (48–62)	94 ± 5 (77–114)
0.05	10–15	9	72 ± 5 (53–102)	71 ± 4 (50–98)	99 ± 3 (86–110)	63 ± 6 (40–107)	59 ± 6‡ (37–102)	94 ± 2 (85–103)
0.07	10–15	9	85 ± 3 (78–102)	82 ± 3 (73–91)	97 ± 2 (90–108)	72 ± 3 (58–82)	71 ± 3 (57–85)	99 ± 2 (91–114)
0.10	10–15	9	79 ± 5 (52–100)	74 ± 5 (47–96)	93 ± 2 (88–102)	64 ± 4 (50–88)	60 ± 3‡ (46–68)	93 ± 4 (72–110)
0.15	10–15	9	72 ± 4 (58–103)	74 ± 5 (60–107)	102 ± 3 (84–100)	66 ± 6 (42–104)	63 ± 6 (44–106)	96 ± 2 (93–115)
0.20	10–15	9	82 ± 5 (65–108)	69 ± 10‡ (31–115)	82 ± 9 (46–120)	72 ± 7 (40–106)	76 ± 7 (42–106)	107 ± 6 (86–141)
0.25	10–15	8	75 ± 3 (65–87)	67 ± 6‡ (45–97)	87 ± 5 (66–100)	56 ± 4 (48–82)	58 ± 4 (50–78)	104 ± 3 (93–117)
0.30	10–15	9	76 ± 3 (62–93)	52 ± 4‡ (37–68)	68 ± 5 (49–80)	71 ± 3 (61–86)	74 ± 4 (61–90)	106 ± 2 (100–115)
0.20	30	9	80 ± 4 (61–94)	78 ± 6§ (48–109)	98 ± 8 (72–100)	61 ± 2 (54–68)	64 ± 3 (50–80)	104 ± 3 (98–118)
0.25	30	9	80 ± 3 (65–93)	75 ± 7 (43–113)	92 ± 8 (65–108)	66 ± 4 (45–80)	67 ± 4 (52–82)	102 ± 3 (91–112)
0.25	60	9	74 ± 3 (59–88)	73 ± 4¶ (55–93)	99 ± 1 (92–102)	63 ± 4 (50–80)	61 ± 4 (48–73)	97 ± 2 (88–111)

* All data given as mean ± SE, with ranges in parentheses. Arterial pressures at 0.03–0.07 mg/kg obtained by oscillotonometry. Pressures at 0.1 mg/kg or more were recorded directly *via* arterial catheter.
† Absolute value at maximum deviation.
‡ $P < 0.017$ *versus* baseline.
§ $P < 0.01$ *versus* 10–15 s bolus.
¶ $P < 0.001$ *versus* 10–15 s bolus.

50% of the subjects; second, as the dose producing 20% or more decrease in mean arterial pressure in 50% of the recipients[2]; and third, as the dose resulting in 100% or greater increase in plasma histamine to levels above 1,000 pg/ml in 50% of the recipients.[6] In this manner, the dose response for histamine-related events was treated in quantal fashion. The ED_{50}s were derived from dose–response curves generated by linear regressions of probit values representing the incidences (percentages) of people responding at each dose of mivacurium. A modification of the original method of Litchfield and Wilcoxon was used.[9]

An average dose ratio (ED_{50} for histamine-related events/ED_{95} for neuromuscular blockade) was calculated, with the use of the average ED_{50} for histamine-related events estimated by the above three methods and the ED_{95} for neuromuscular blockade (0.08 mg/kg) previously reported.[1]

Data Analysis

Arterial pressure and heart rate trend analysis was done by repeated measures analysis of variance (ANOVA) followed by paired *t* test with the Bonferroni correction[10] for multiple comparisons.

Plasma histamine and mean arterial pressure changes were correlated by linear regression.

Intragroup comparisons of plasma histamine changes were completed by analysis of variance. Intergroup comparisons of peak (2 min) histamine levels were done by Student's *t* test for unpaired values.

Differences were considered statistically significant when $P < 0.05$ or, when using the Bonferroni correction, $P < 0.017$, where n = 3 comparisons to control heart rate and arterial pressure during the first 3 min after mivacurium injection.

Results

Data are expressed as mean ± SE (range) unless otherwise specified. Data are summarized in tables 1 and 2 and in figures 1–5.

Electrocardiogram

No rhythm disturbances were noted.

Heart Rate

The average maximum deviation in heart rate was 7% or less from control after all doses of mivacurium (table 1, fig. 1).

TABLE 2. Plasma Histamine Concentration Changes and Incidence and Duration of Histamine-related Phenomena after Initial Doses* of Mivacurium

Dose (mg/kg)	Injection Rate (s)	Plasma Histamine n	Plasma Histamine Control (pg/ml + SE)	Plasma Histamine 2 Minutes Postmivacurium (pg/ml + SE)	Incidence of Facial Erythema†	Incidence of Plasma Histamine Increase > 100% to >1,000 pg/ml	Incidence of Decline of Mean Arterial Pressure <80% of Control†	Duration (min) of MAP < 80% of Control
0.10	10–15	8	548 ± 120 (298–1,159)	362 ± 71 (179–797)	0/9	0/8	0/9	—
0.15	10–15	9	613 ± 210 (109–2,138)	990 ± 357 (101–2,902)	1/9	3/9	0/9	—
0.20	10–15	8	756 ± 245 (113–2,279)	1,470 ± 548 (103–3,904)	2/9	3/8	4/9	1.16 ± 0.52 (0.3–2.2)
0.25	10–15	7	881 ± 240 (276–2,121)	1,163 ± 315 (321–2,506)	6/9	2/6	4/8	0.30 ± 0.15 (0.5–1.0)
0.30	10–15	9	312 ± 86 (160–990)	2,266 ± 730‡ (228–6,303)	6/9	6/9	7/9	0.37 ± 0.09 (0.2–4.5)
0.20	30	9	704 ± 217 (148–2,082)	727 ± 97 (231–1,102)	2/9	1/9	3/9	0.56 ± 0.12 (0.4–0.8)
0.25	30	8	687 ± 222 (252–2,039)	1,453 ± 478 (178–4,275)	3/9	4/8	3/9	0.67 ± 0.27 (0.3–1.2)
0.25	60	9	425 ± 109 (111–958)	421 ± 88§ (144–818)	0/9	0/8	0/9	—

* All values ± SE. Ranges given in parentheses.
† Sample size in some groups is higher than n for histamine data because histamine levels were not obtained in all cases.
‡ $P < 0.001$ *versus* baseline.
§ $P < 0.001$ *versus* 10–15 s bolus.

ARTERIAL BLOOD PRESSURE AND PLASMA HISTAMINE: INJECTION OVER 10–15 S

After doses up to and including 0.15 mg/kg mivacurium (about 2 × ED_{95}), the average maximum change in mean arterial pressure was 7% or less. When mivacurium was injected over 10–15 s at 0.20, 0.25, and 0.30 mg/kg, a decrease in mean arterial pressure was noted that averaged 18, 13, and 32%, respectively (table 1, fig. 1). In individual subjects, the depressor response lasted 0.2–4.5 min (table 2).

Average plasma histamine levels did not change significantly after injection of 0.10–0.25 mg/kg mivacurium over 10–15 s. An upward trend of average plasma histamine level was evident, however, in samples obtained 2 min after injection over 10–15 s of mivacurium, 0.15–

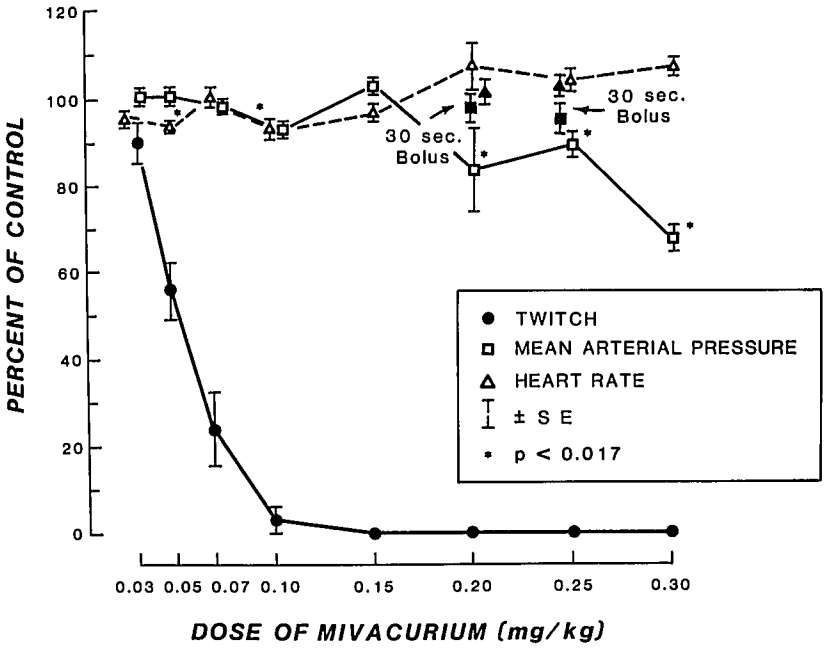

FIG. 1. Neuromuscular and cardiovascular dose–response of mivacurium after injection over 10–15 s. Points represent mean peak changes within each group of eight or nine patients. Cardiovascular effects (black squares and triangles) after slower injection (over 30 s) of 0.20 and 0.25 mg/kg are included for comparison. See text for further details.

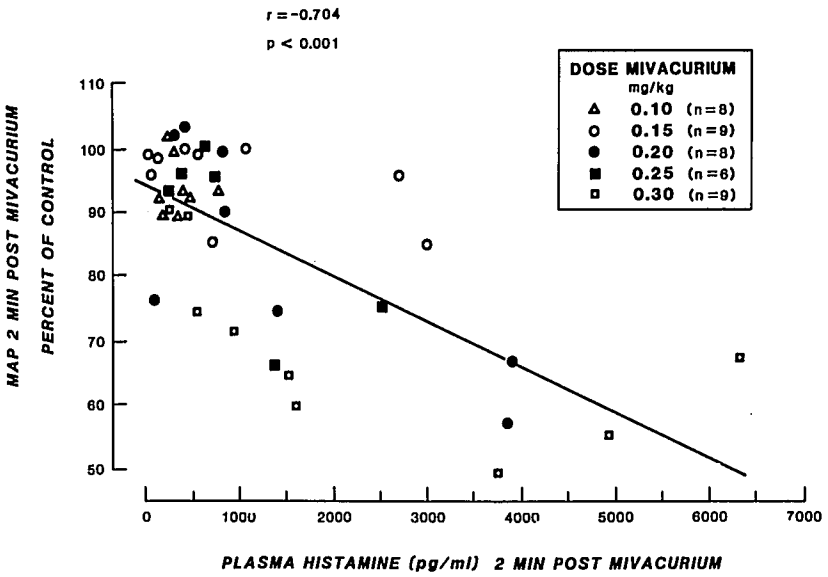

FIG. 2. Relationship between individual peak plasma histamine concentrations and decreases in blood pressure after injection over 10–15 s of doses of mivacurium above ED_{95}.

0.30 mg/kg. This increase became statistically significant ($P < 0.05$) at 4 × ED_{95} or 0.30 mg/kg (see table 2), the highest dose of mivacurium studied. The increase was transient, however, because mean levels obtained 5 min after drug injection were once again within normal limits. In individual subjects, on the other hand, the relationship of decrease in arterial blood pressure to increase in plasma histamine was highly significant (fig. 4, r = −0.704, $P < 0.001$).

The average decrease in mean arterial pressure after mivacurium doses from 0.20 to 0.30 mg/kg therefore includes a number of people in each group who showed a brief vasodepressor response (table 2 and fig. 3A). All other subjects had little or no change in pressure develop

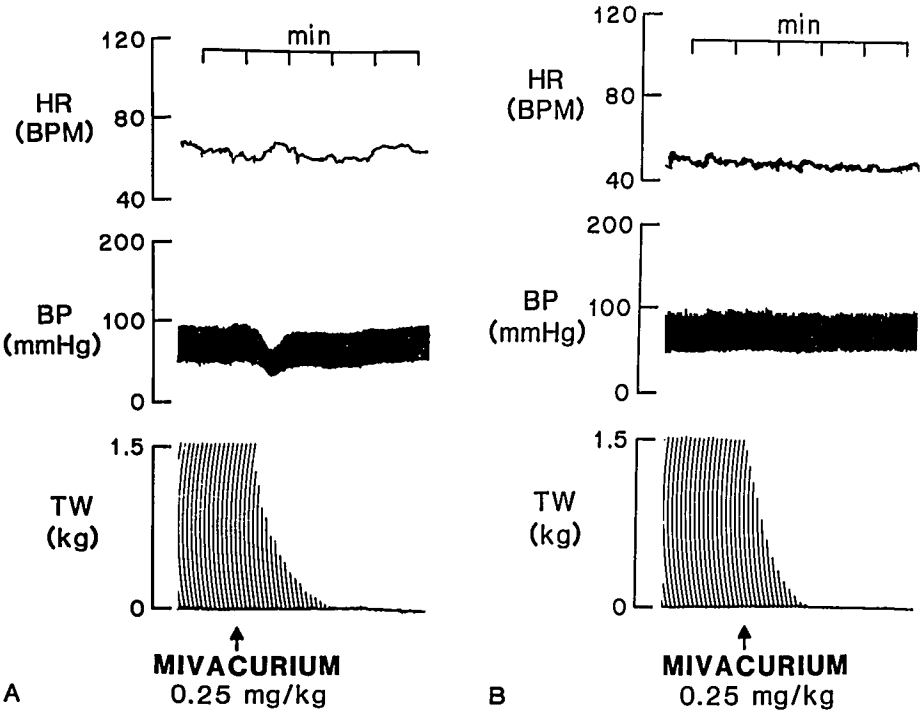

FIG. 3. *A* (left). Onset of neuromuscular blockade and evolution of cardiovascular changes in a patient who received 0.25 mg/kg mivacurium over 10–15 s. Time scale at top; calibrations at left. Thumb adduction (TW) was evoked at 0.15 Hz *via* the ulnar nerve at the wrist. Blood pressure (BP) was recorded *via* radial arterial cannula. Heart rate was counted by tachograph from the arterial pulse wave. This individual response is typical of the four patients (50% of subjects) who manifested 20% or more decrease in mean arterial pressure after 10–15 injection of 0.25 mg/kg. *B* (right). Recording from another patient as in *A*. This subject also received 0.25 mg/kg mivacurium over 10–15 s. Four of eight patients who received this dose at this rate as well as all nine who received it as a slower injection over 60 s showed minimal cardiovascular response.

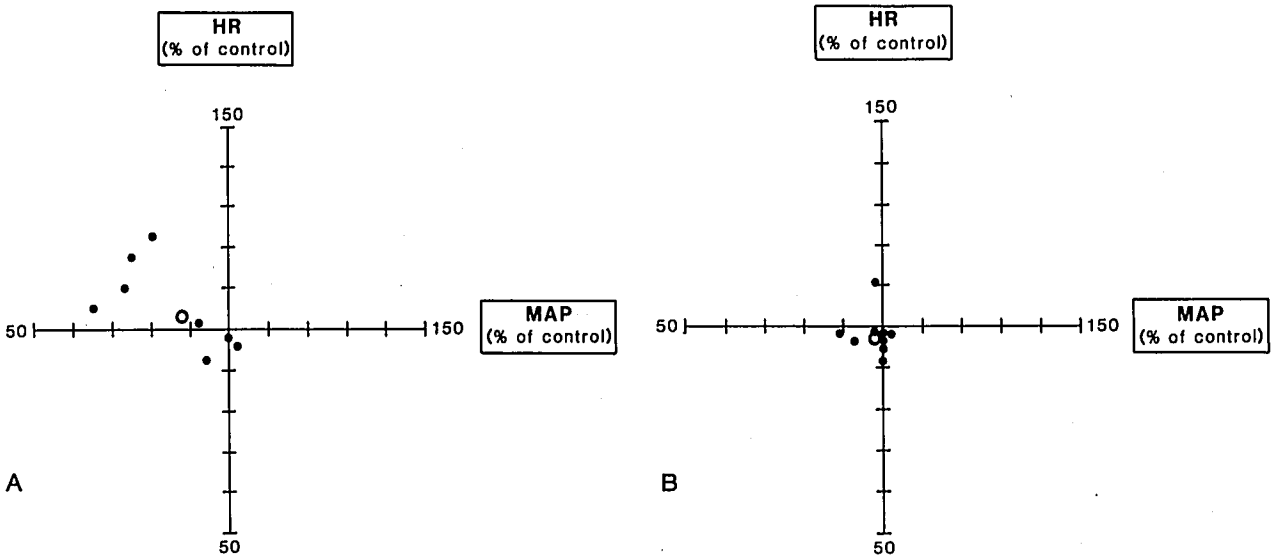

FIG. 4. *A* (left). Scatter plot of maximal individual cardiovascular responses after injection of mivacurium, 0.25 mg/kg over 10–15 s. Intersection of x- and y-axes (origin) represents the point of no change in heart rate or blood pressure. Each dot represents one person's response. Open circle indicates the group mean response. *B* (right). Scatter plot of maximal individual cardiovascular responses as in *A*, after injection of mivacurium, 0.25 mg/kg, over 60 s.

(fig. 3B). Individual responses within groups are readily apparent in scatter plots. For example, at 0.25 mg/kg (fig. 4A), four of eight patients who received this dose over 10–15 s manifested decreases in blood pressure of 22–34% and increases in heart rate of 5–22%. The temporal change in blood pressure and heart rate in this same group as a whole is apparent in the trended normalized data (fig. 5A).

ARTERIAL BLOOD PRESSURE AND PLASMA HISTAMINE: INJECTION OVER 30 OR 60 S

In three additional groups of patients (n = 9 each) who received 0.20 or 0.25 mg/kg mivacurium over 30 or 60 s, the decreases in blood pressure and increases in plasma histamine were attenuated. When 0.20 mg/kg was given over 30 s or when 0.25 mg/kg was injected over 60 s,

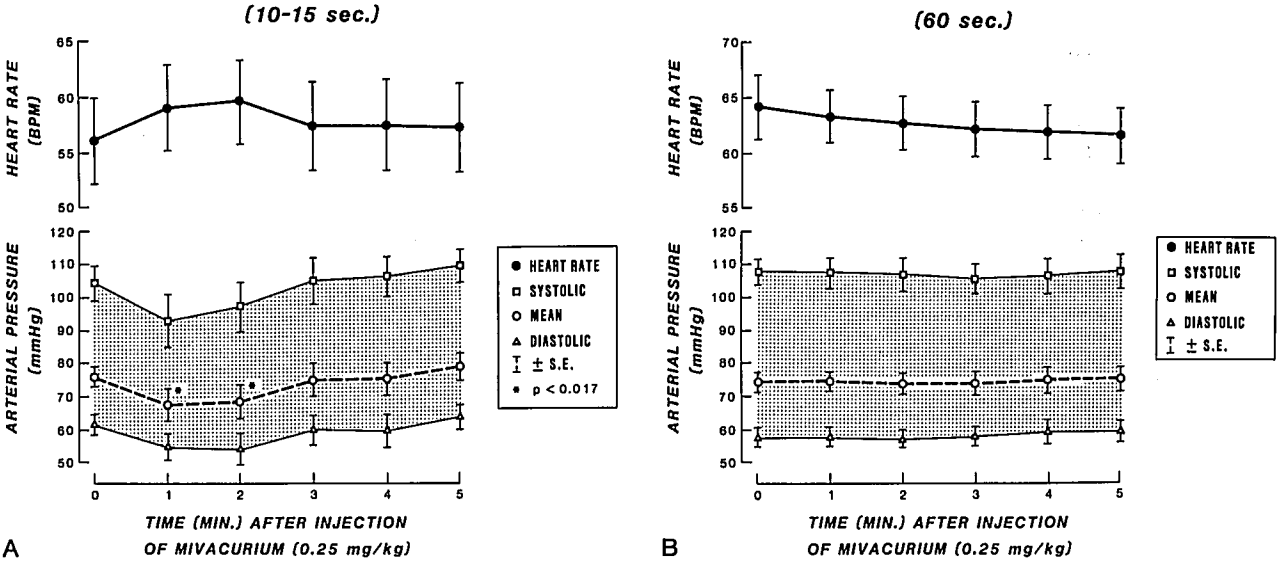

FIG. 5. *A* (left). Trended group cardiovascular responses after administration of mivacurium, 0.25 mg/kg, over 10–15 s. *B* (right). Trended group cardiovascular responses after injection of mivacurium, 0.25 mg/kg, over 60 s.

group changes in mean arterial pressure and plasma histamine did not achieve statistical significance ($P > 0.05$ by ANOVA) (see tables 1 and 2). When compared with the data after 10–15-s injection, the difference in maximum change is significant ($P < 0.001$ in both cases). Although data obtained after injection of 0.25 mg/kg over 30 s show a similar trend, the differences *versus* injection over 15 s were not significant. No one who received 0.25 mg/kg over 60 s showed any hemodynamic change of more than 10% (fig. 4B).

Arterial Blood Pressure: Second Dose Given over 10–15 s

Average mean blood pressure, which decreased to 82 and 87% of baseline, respectively, after initial doses of 0.20 and 0.25 mg/kg mivacurium injected over 10–15 s, decreased only to 98 and 92% of control, respectively, after second doses given at that rate. The difference in blood pressure change was significant when first and second doses were compared in the group that received 0.20 mg/kg twice ($P < 0.05$ by paired t test) but not in the group that was given 0.25 mg/kg twice.

Dose Ratio: ED_{50} for Histamine-Related Events/ED_{95} for Neuromuscular Blockade

This safety ratio was calculated based upon the incidence of histamine-related phenomena listed in table 2.

The derived ED_{50} values (95% confidence limits in parentheses) for histamine-related phenomena were as follows: 1) based on incidence of facial erythema: 0.241 mg/kg (0.202–0.288); 2) based on incidence of 20% or more decrease in mean arterial pressure: 0.235 mg/kg (0.193–0.285); 3) based on incidence of 100% or greater increase in plasma histamine to levels above 1,000 pg/ml: 0.253 mg/kg (0.185–0.347).

The three estimates do not differ significantly. The average of the above estimates is 0.243 mg/kg. The dose ratio (ED_{50} for histamine-related events/ED_{95} for neuromuscular blockade) is 0.243/0.08 or 3.0. This ratio, obtained under conditions in which mivacurium is injected over 10–15 s, increases to greater than 3.0 when injection is done more slowly. For example, after 60-s injection of 0.25 mg/kg mivacurium, blood pressure and plasma histamine did not change significantly, and the incidence of facial erythema was zero (tables 1 and 2).

Discussion

The data indicate that the cardiovascular effects of mivacurium may become evident after injection over 10–15 s of doses greater than $2 \times ED_{95}$. The principal effect that may occur is a transient decrease in blood pressure. This likely results from a dose-related release of histamine because elevations of plasma levels of this substance in individual subjects correlate well not only with decreases in blood pressure but also with incidence of facial erythema (tables 1 and 2). Two observations further supporting this mechanism are as follows: 1) the development of tachyphylaxis to decrease in blood pressure on repeat dosing with mivacurium; and 2) amelioration of this cardiovascular effect and reduction of the increase in plasma histamine concentration by slowing the rate of injection of mivacurium, *e.g.*, 30-s injection at 0.20 mg/kg and 60-s injection at 0.25 mg/kg (tables 1 and 2, and figs. 3–5).

A statistically significant decrease in heart rate was noted after injection of 0.05 and 0.10 mg/kg mivacurium over 10–15 s. This change is probably insignificant to clinical practice and may reflect the development of opiate-induced bradycardia during nitrous oxide anesthesia.

Benzylisoquinolinium compounds such as mivacurium are well known to have the potential for releasing histamine.[11] The prominence of the side effect is reflected in the dose ratio comparing ED_{95} for neuromuscular blockade with an effective dose (ED_{50}) for a specific end point for increase in plasma histamine or for indicators of histamine release such as 20% or greater decrease in arterial pressure and/or obvious facial erythema.[2,4,6,8,11,12] A ratio of 3.0 for mivacurium in humans suggests that the order of likelihood of observation of such phenomena is *d*-tubocurarine > metocurine > atracurium > mivacurium > doxacurium.[3,6,8,12]

In the present study, analysis of histamine-related phenomena as a dose response was made possible by defining criteria where the response attains clinical relevance in an individual subject. These end points were as follows: development of obvious facial erythema, a 20% decrease in mean arterial pressure, and a 100% or greater increase in plasma histamine to 1,000 pg/ml (*i.e.*, abnormally high levels). The data was then treated in quantal fashion. This approach seems reasonable, because the three-dose–response curves were similar, resulting in nearly identical ED_{50} estimates.

Two cholinergic pathways may be blocked by nondepolarizing relaxants. These include nicotinic transmission through ganglia and muscarinic transmission through postganglionic parasympathetic junctions in the pacemaker system of the heart.[2,13] Autonomic margin-of-safety ratios[2] for inhibition of these mechanisms by mivacurium in the cat are at least 200 and 36, respectively (Wastila WB, Maehr B, Savarese JJ, unpublished data). Consequently, the dose required to cause these pharmacologic effects in humans is probably well beyond the clinical range. Therefore, any cardiovascular changes observed during clinical administration of mivacurium should most likely result from the histamine-releasing property.

Histamine's effects on the cardiovascular system, particularly as a result of endogenous release of the substance

by neuromuscular blocking drugs, have been reviewed by Moss and Rosow.[11] Histamine has a positive inotropic and chronotropic effect on the heart *via* myocardial H_2 receptors. Part of this effect may result from histamine-stimulated liberation of myocardial catecholamines.[11] Increases in heart rate accompanying other clinical manifestations of liberation of histamine such as skin flushing and decrease in blood pressure probably result from these myocardial effects as well as a carotid-sinus–mediated reflex response to histamine-induced peripheral vasodilation.[14] The transient increases in heart rate noted herein after mivacurium dosage in the 0.20–0.30 mg/kg range should have occurred as a result of these combined mechanisms. Because release of histamine appears to be the principal mechanism underlying any decrease in blood pressure induced by mivacurium, it seems unlikely that a myocardial depressant effect might be considered a causative factor.[14] Most likely the cause is peripheral venous and arteriolar dilation *via* stimulation of vascular H_1 and H_2 receptors. Other substances liberated by mast-cell degranulation, such as vasoactive polypeptides (kinins) or arachidonic acid derivatives (prostaglandins), may also play a role.[14]

The relationship of size of dose and speed of injection to the cardiovascular response after mivacurium administration may be more important during clinical administration of mivacurium than in the case of other nondepolarizing relaxants. This may be the case because the duration of action of mivacurium increases least among nondepolarizers as dosage is augmented. This feature allows injection of larger doses to speed onset, increasingly facilitating earlier tracheal intubation without significantly lengthening paralysis.[15–19] Recovery of twitch should begin within about 15 min and reach 95% of control and train-of-four ratio of 70% after these doses within approximately 30 min after injection.[1,15–19] By comparison, after large doses of atracurium (0.8–1.5 mg/kg) or vecuronium (0.25 mg/kg), which allow tracheal intubation within 60–90 s after injection, recovery begins within approximately 60–80 min.[20,21]

Although increasing the dose of mivacurium to speed onset has little effect on duration of block, the cardiovascular effects are intensified as dosage is increased beyond 0.15 mg/kg. Although transient in healthy patients, they may be clinically important in such patients as these with coronary artery disease, particularly those receiving diuretics or beta-adrenergic blocking drugs. In such cases, injection over 10–15 s or faster might cause a longer-lasting decrease in blood pressure resulting from diuretic-induced reduced intravascular volume or beta-blocker-induced inhibition of compensatory reflexes to the peripheral vasodilating effect of histamine.

In situations in which one might wish to reduce the side effects, slower injection of mivacurium or administration of mivacurium by infusion would seem advisable, because the hemodynamic effect is reduced by injection over 30–60 s. This is true in the case of other related substances such as atracurium, BW A444U, and BW 785U.[4,11,20,22] Alternatively, prophylaxis with combined H_1 and H_2 blockers is also well known to shift the cardiovascular dose–response to the right in the case of both relaxants[11,22] and opiates,[11,23] which may cause a decrease in blood pressure as a result of release of histamine. In any event, hemodynamic studies of mivacurium in patients with cardiovascular disease are needed in order to provide specific guidelines for its administration to these patients.

It is well known that succinylcholine-induced bradycardia may develop, particularly after repeat doses.[24] On the other hand, amelioration of the cardiovascular effect of mivacurium during repetitive dosage is a noteworthy contrast between the two drugs.

We conclude that the cardiovascular response to mivacurium in ASA physical status I–II surgical patients is minimal after doses up to and including 0.15 mg/kg ($2 \times ED_{95}$). A decrease in blood pressure may occur in some individuals after initial injection over 10–15 s of higher doses (0.20, 0.25, and 0.30 mg/kg). The incidence and the magnitude of this response are related to size of dose and to speed of injection. The decrease in blood pressure is directly related to increase in plasma histamine concentration. The dose ratio (ED_{50} for histamine-related events/ED_{95} for neuromuscular blockade)[2] after injection over 10–15 s is 3.0, or about three times that of *d*-tubocurarine and similar to that of atracurium.[3,6,8,11] The ratio may be increased by slowing the rate of injection of mivacurium.

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