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The Cardiovascular Effects and Histamine-releasing Properties of 51W89 in Patients Receiving Nitrous Oxide/Opioid/Barbiturate Anesthesia

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Background: **Atracurium consists of a mixture of ten stereoisomers. One of these isomers, 51W89, is a potent intermediate-acting nondepolarizing neuromuscular blocking agent. Its ED_{95} is 0.05 $mg \cdot kg^{-1}$ in patients receiving nitrous oxide/opioid anesthesia. In preclinical trials, 51W89 did not show evidence of histamine release in cats at doses up to 80 times the human ED_{95}. This study was undertaken to determine the cardiovascular effects and histamine-releasing properties of 51W89 in patients undergoing elective surgical procedures.**

Methods: **Sixty patients, ASA physical status 1 or 2, anesthetized with nitrous oxide/fentanyl/thiopental were studied. Patients received either 2 times the ED_{95} of atracurium or 51W89 or 4 or 8 times the ED_{95} of 51W89 as a rapid intravenous bolus under stable anesthesia, before surgical stimulation. Blood pressure and heart rate were measured by oscillometry and the electrocardiogram in patients receiving 2 times the ED_{95} of 51W89 or atracurium and by an intraarterial catheter and a tachograph triggered by the arterial pulse waveform in patients receiving 4 or 8 times the ED_{95} of 51W89. Maximal blood pressure and heart rate changes during the 5 min after administration of the muscle relaxant were recorded. Venous blood samples were obtained before the administration of relaxant and at 2 and 5 min after the administration of relaxant for determination of plasma histamine concentrations by radioenzymatic assay.**

Results: **Maximal blood pressure and heart rate changes in all groups of patients receiving 51W89 were small and similar to those observed in patients receiving 2 times the ED_{95} of atracurium. The mean maximum percent changes (± SE) in heart rate and mean arterial pressure were −0.6 ± 1.5 and 0.4 ± 2.5, respectively, in the group receiving 2 times the ED_{95} atracurium; −1.3 ± 3.3 and 2.3 ± 4.4, respectively, in the group receiving 2 times the ED_{95} 51W89; −2.6 ± 1.0 and 2.6 ± 1.5, respectively, in the group receiving 4 times the ED_{95} 51W89; and −2.4 ± 1.5 and −1.0 ± 1.3, respectively, in the group receiving 8 times the ED_{95} 51W89. No patient developed a decrease in blood pressure ≥20% or an increase in heart rate ≥20% that was attributable to muscle relaxant administration. There was no dose-related change in plasma histamine concentration associated with the administration of 51W89. One patient in the study developed transient facial flushing after the administration of atracurium.**

Conclusions: **51W89 is a benzylisoquinolinium-type, nondepolarizing muscle relaxant that does not affect plasma histamine concentrations. No cutaneous flushing or clinically important cardiovascular effects were noted after rapid injection of doses up to and including 8 times its ED_{95} (0.4 $mg \cdot kg^{-1}$) in healthy patients undergoing elective surgical procedures. (Key words: Neuromuscular relaxants, 51W89: cardiovascular effects; histamine.)**

51W89, which has a 1 *R-cis,* 1′ *R-cis* configuration, is one of the ten stereoisomers of atracurium, comprising approximately 15% of the atracurium mixture. This compound is a potent, nondepolarizing neuromuscular blocking agent with an intermediate duration of action.[1] Its ED_{95} for neuromuscular block in patients receiving nitrous oxide/opioid/barbiturate anesthesia is 0.05 $mg \cdot kg^{-1}$.[1,2] As one of the isomers of atracurium, this compound presumably undergoes Hoffman elimination and ester hydrolysis. Its clearance and elimination half-life are similar to those of atracurium.[3]

Bisbenzylisoquinolinium compounds, in general, tend to cause histamine release, which can result in

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facial flushing and hemodynamic aberrations.[4–8] The cardiovascular effects normally noted secondary to histamine release are a decrease in mean arterial pressure and a compensatory increase in heart rate. These responses normally are transient and are related to both the size of the dose of relaxant administered and the time course over which the dose is given. The tendency of a bisbenzylisoquinolinium to cause histamine release may be estimated by the quotient of the dose of relaxant required for histamine release divided by the ED_{95} of the relaxant for neuromuscular block. This quotient, or safety ratio, ranges from 1 for d-tubocurarine[4,8] to 1.5–2 for metocurine to 2–3 for atracurium[5] and mivacurium.[7] Administration of large doses of these relaxants over 30–60 s, rather than over 5 s, will attenuate the hemodynamic changes associated with their rapid administration.[7] Doxacurium, the extremely potent, long-acting muscle relaxant, is, to date, the only bisbenzylisoquinolinium not associated with histamine release.[9–11]

In preclinical trials, doses of 51W89 as large as 64 times the ED_{95} did not produce histamine-like cardiovascular effects or increased plasma histamine concentration in cats.[12] Twenty-one times its ED_{95} for neuromuscular block in monkeys had minimal cardiovascular effects.[13] Furthermore, doses up to 27 times the ED_{95} did not have autonomic side effects in cats.[12] Thus, preclinical data suggested that 51W89 might cause minimal cardiovascular responses after large doses in human subjects. This study was undertaken to determine the cardiovascular effects and histamine-releasing properties of 51W89 in generally healthy patients undergoing elective surgical procedures under nitrous oxide/opioid/barbiturate anesthesia.

Methods

Patient Selection

After obtaining approval from the Committee on Human Rights in Research of Cornell University Medical College-New York Hospital and signed informed consent, 60 patients ranging in age from 20 to 65 yr were studied. All patients were ASA physical status 1 or 2 and were scheduled to undergo elective minor surgical procedures. Patients were free of neuromuscular, hepatic, renal, pulmonary, or cardiovascular disease. None had a history of unusual susceptibility to neuromuscular blocking agents or malignant hyperthermia. No patient had received antibiotics with the exception of penicillin, cephalosporins, or tetracyclines within the 48 h before their enrollment in the study. No anticonvulsants, antidepressants, or antihistamines were given within the week before the study. Female patients were not pregnant or were not of childbearing potential.

On consenting to participate in the study, the first 30 patients were randomly assigned to receive either 2 times the ED_{95} of 51W89 or 2 times the ED_{95} of atracurium, with 15 patients enrolled into each group. The next 15 patients were assigned to receive 4 times the ED_{95} of 51W89 and the final 15 patients were assigned to receive 8 times the ED_{95} of 51W89.

Anesthetic Management and Patient Monitoring

In the operating room, intravenous access was established, and electrocardiograms, blood pressure cuffs, and pulse oximeters were used for routine monitoring. While patients breathed 100% O_2 through an anesthesia face mask, general anesthesia was induced with intravenous midazolam (20–100 $\mu g \cdot kg^{-1}$), fentanyl (2–8 $\mu g \cdot kg^{-1}$), and thiopental (1–10 $mg \cdot kg^{-1}$). The patients' tracheas were intubated before the administration of 51W89 or atracurium, and anesthesia was maintained with oxygen (30%), nitrous oxide (70%), and additional doses of intravenous fentanyl, midazolam, and thiopental as required. Mechanical ventilation was adjusted to maintain normocapnia.

Esophageal temperature was maintained between 34.3°C and 36.5°C with warmed intravenous fluids, blankets, and gas humidifiers. After the induction of anesthesia, a second intravenous catheter was inserted in all patients for venous blood sampling, and a 20-G intraarterial catheter was inserted in patients scheduled to receive either 4 or 8 times the ED_{95} of 51W89 for continuous blood pressure monitoring. All patients receiving a dose of 51W89 greater than 2 times its ED_{95} had their heart rate recorded continuously by a Grass 7P44 tachograph triggered by the arterial pulse waveform. For patients receiving a dose of either 51W89 or atracurium at 2 times the ED_{95}, blood pressure was measured by oscillometry (Dinamap) at 1-min intervals for at least 3 min before and 5 min after the administration of the relaxant. In these patients, heart rate was determined from the electrocardiogram (Marquette model 700 or 710).

The ulnar nerve was stimulated at the wrist through 23-G steel needle electrodes with a supramaximal

square wave impulse of 0.2 ms duration. The stimulus was delivered at a frequency of 0.15 Hz from a Grass S88 stimulator in conjunction with a force displacement transducer (Grass model FT-10) applied to the thumb and recorded on a Grass Model 7 polygraph.

Muscle Relaxant Administration

After at least 3 min of stabilization of the response to neuromuscular stimulation and at least 3 min of stable baseline heart rate and blood pressure measurements, patients received, as a 5-s bolus and into a rapidly flowing intravenous line, 0.5 $mg \cdot kg^{-1}$ atracurium (2 times the ED_{95}), 0.1 $mg \cdot kg^{-1}$ 51W89 (2 times the ED_{95}), 0.2 $mg \cdot kg^{-1}$ 51W89 (4 times the ED_{95}), or 0.4 $mg \cdot kg^{-1}$ 51W89 (8 times the ED_{95}), depending on the study group into which they were enrolled. During the 5 min after completion of administration of the muscle relaxant, blood pressure and heart rate were monitored as described previously. Patients also were monitored during this time for cutaneous flushing. Thereafter, blood pressure and heart rate were monitored as appropriate clinically. Surgery was not begun for at least 5 min after the administration of muscle relaxant.

Determination of Plasma Histamine Concentrations

Three 5-ml venous blood samples were obtained just before and 2 and 5 min after the administration of the initial bolus dose of relaxant. Each sample was placed, within 5 s, into a chilled polypropylene tube containing 50 μl of EDTA. Within 5 min, the tube was centrifuged, and then 1–2 ml of plasma was separated and transferred to a chilled propylene tube. The tube was then frozen over dry ice and stored at −70°C until later analysis for plasma histamine concentrations. Samples were assayed promptly for plasma histamine concentrations in the research laboratories of the Massachusetts General Hospital, using a radioenzymatic assay based on the detection of tritiated N-methylhistamine formed from histamine and [^{3}H-]S-adenosyl-L-methionine in the presence of purified histamine N-methyltransferase.[14] The assay has a sensitivity of 2.2 $pcg \cdot ml^{-1}$ and a specificity of 0.01%, except in the presence of N-α-methylhistamine. In the presence of equimolar concentrations of N-α-methylhistamine, the assay has a specificity of 4%. The assay is linear from 2.2 pcg to 1 ng.

Data Analysis

Mean arterial pressure was calculated for the patients receiving 2 times the ED_{95} of 51W89 or atracurium using the formula: MAP = $^1/_3$ (systolic pressure) + $^2/_3$ (diastolic pressure). Mean arterial pressure and heart rate data were recorded as actual values and as percentage changes from baseline values. In addition, the value representing the maximum change during the first 5 min after the initial dose of 51W89 or atracurium was identified. Clinically significant changes were defined as deviations of more than 20% from baseline values. Unless clinically significant changes in mean arterial pressure or heart rate occurred, only patients having both preinjection values and a minimum of three postinjection values for mean arterial pressure or heart rate were included in this analysis. If a maximum increase and decrease of equal magnitude were observed in the first 5 min, the decrease from baseline was adopted as the maximum change for mean arterial pressure, whereas the increase from baseline value was adopted for heart rate.

Two approaches were used to analyze heart rate and blood pressure data after the initial dose of 51W89 or atracurium. Summary statistics were generated, by group, for mean heart rate and mean arterial pressure (expressed as a percentage of baseline) at the time of maximum change. In addition, the maximum percentage change in mean arterial pressure was plotted against the maximum change in heart rate for each patient by group.

Demographic data were compared among study groups using Fisher's two-tailed exact test or analysis of variance, as appropriate. Anesthetic doses among study groups were compared using analysis of variance with Duncan's multiple range test. $P < 0.05$ was considered statistically significant. All results are presented as mean ± SE.

Results

As shown in table 1, there were no significant differences among the study groups with respect to age or race. Patients who received either 4 or 8 times the ED_{95} of 51W89 tended to be taller and heavier than patients receiving 2 times the ED_{95} of either atracurium or 51W89. All patients were within 20% of their ideal body weight. The study groups also differed in terms of their gender composition in that all of the patients receiving either 4 or 8 times the ED_{95} of 51W89 were male. There were no significant differences among the groups with respect to the total dose of fentanyl or midazolam administered before the relaxant, as shown

Table 1. Patient Demographics

	Atracurium $2 \times ED_{95}$	51W89 $2 \times ED_{95}$	51W89 $4 \times ED_{95}$	51W89 $8 \times ED_{95}$	*P* Value
Age (yr)	39.9 ± 2.1	37.8 ± 2.7	38.8 ± 2.0	35.3 ± 1.8	0.5
Weight (kg)	76 ± 2	74 ± 4	86 ± 3	87 ± 2	0.001
Height (cm)	174 ± 2	172 ± 3	180 ± 2	182 ± 1	0.004
Gender (% female/% male)	20/80	40/60	0/100	0/100	0.004
Race (% black/% white/% other)	13/73/13	13/73/13	7/80/13	7/93/0	0.8

Values for age, weight and height are mean ± SE; n = 15 in each study group.
$P < 0.05$ is significant.

in table 2. Patients receiving 2 times the ED_{95} of 51W89 received significantly more thiopental than did patients receiving either 4 or 8 times the ED_{95} of the relaxant, 6 $mg \cdot kg^{-1}$ compared to 4 $mg \cdot kg^{-1}$, respectively.

The neuromuscular pharmacology of 51W89 is presented in detail elsewhere.[15] All patients in the four study groups developed 100% neuromuscular block after the administration of the relaxant.

As shown in figure 1, there were no dose-related changes in mean arterial pressure or heart rate associated with the administration of any dose of 51W89. The averages of the maximal changes in heart rate and mean arterial pressure were small in all of the study groups (table 3). As demonstrated in figure 2, only two patients in the study developed greater than 20% decreases in mean arterial pressure or greater than 20% increases in heart rate. The mean arterial pressure of one patient who received 2 times the ED_{95} of 51W89 transiently decreased by 22% from his baseline, from 100 to 78 mmHg, and his heart rate decreased by 4%, from 67 to 64 beats/min. This decrease in mean arterial pressure occurred at 2 min after the administration of 51W89 and persisted for 2 min. Five minutes after the administration of 51W89, his mean arterial pressure had increased to 84 mmHg. Heart rate in another patient who received 2 times the ED_{95} of 51W89 transiently increased by 33% above his baseline heart rate, from 51 to 68 beats/min 3 min after the administration of relaxant, and his blood pressure increased by 24%, from 76 to 94 mmHg. One minute later, however, his heart rate had decreased to 53 beats/min, and his mean arterial pressure to 85 mmHg. No patients receiving greater than a 2 times the ED_{95} dose of 51W89 experienced heart rate or mean arterial pressure changes $\geq$20% of their baseline values. The largest blood pressure and heart rate changes seen in these patients were a decrease in heart rate of 16% in a patient receiving 8 times the ED_{95} of 51W89 and an increase in mean arterial pressure of 14% in a patient receiving 4 times the ED_{95} of 51W89.

One patient experienced transient facial flushing after the administration of atracurium. However, he did not experience hypotension or tachycardia and did not exhibit increased plasma histamine levels at 2 or 5 min after the administration of relaxant.

As shown in figure 3, there were no dose-related changes in plasma histamine concentrations after the administration of 51W89. Transient doubling of plasma histamine concentrations to values in the range of 1,000–2,000 $pg \cdot ml^{-1}$ was observed in two patients

Table 2. Intravenous Anesthetic Doses before Administration of Muscle Relaxant

	Atracurium $2 \times ED_{95}$	51W89 $2 \times ED_{95}$	51W89 $4 \times ED_{95}$	51W89 $8 \times ED_{95}$	*P* Value
Fentanyl (μg/kg)	4.6 ± 0.3	4.9 ± 0.4	4.5 ± 0.3	5.1 ± 0.4	0.6
Midazolam (μg/kg)	52.4 ± 4.5	51.8 ± 4.2	48.3 ± 4.3	46.1 ± 2.2	0.6
Thiopental (mg/kg)	5.2 ± 0.2	6.0 ± 0.4	4.0 ± 0.6	3.9 ± 0.4	0.003

Values are mean ± SE. $P < 0.05$ is significant.

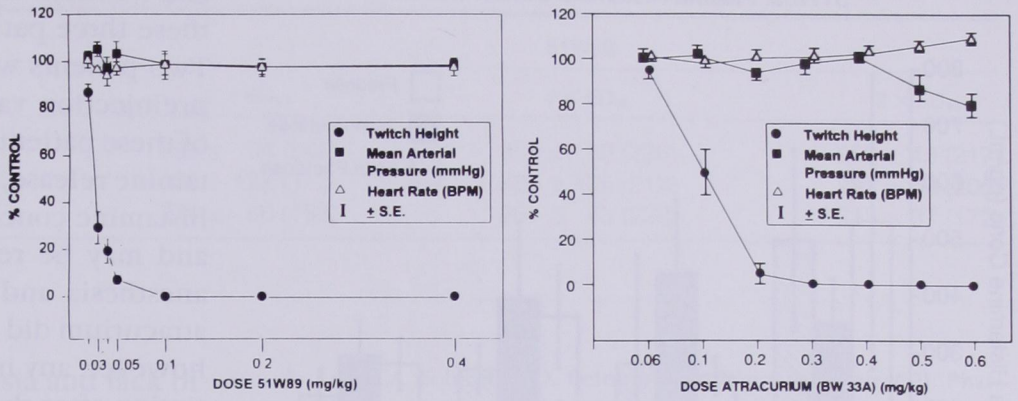

Fig. 1. Mean neuromuscular, heart rate, and blood pressure responses to various doses of 51W89 are shown on the left side of the figure. The data presented for doses at <2 times the ED_{95} of 51W89 are described in another manuscript.[15] Neuromuscular and cardiovascular effects of atracurium (BW 33A)[5] from a previous study are shown on the right side of the figure. Although significant decreases in blood pressure and increases in heart rate are seen with doses ≥2 times the ED_{95} of atracurium, no significant changes are seen in heart rate or blood pressure after doses as large as 8 times the ED_{95} of 51W89.

receiving 2 times the ED_{95} of 51W89 and in one patient receiving 4 times the ED_{95} of 51W89. None of these patients exhibited clinical signs indicative of histamine release, such as cutaneous flushing, decrease in blood pressure, and increase in heart rate. As summarized in table 4, there was a greater median percentage increase in histamine concentrations after 0.5 $mg \cdot kg^{-1}$ atracurium than after any of the doses of 51W89. Two patients receiving atracurium had high levels of plasma histamine before the administration of muscle relaxant. These values remained elevated at 2 and 5 min after atracurium.

Discussion

The results of this study suggest that the administration of 51W89 in doses up to and including 8 times the ED_{95} does not result in dose-dependent histamine release or cardiovascular side effects in healthy patients undergoing elective surgical procedures during nitrous oxide/opioid/barbiturate anesthesia. In this study, all patients received either 51W89 or atracurium as a rapid intravenous bolus in 5 s to maximize the chances of observing histamine release. To minimize the possibility of other factors contributing to increased plasma histamine levels, baseline blood samples were not ob-

Table 3. Mean Blood Pressure and Heart Rate Values before and after Administration of Muscle Relaxant

Study Group	Variable	Baseline Value	Value at Time of Maximum Change
51W89			
2 × ED_{95}	MAP	75 ± 3	76 ± 3
	HR	64 ± 4	63 ± 4
4 × ED_{95}	MAP	77 ± 3	79 ± 3
	HR	64 ± 3	62 ± 2
8 × ED_{95}	MAP	77 ± 2	76 ± 2
	HR	68 ± 3	66 ± 2
Atracurium			
2 × ED_{95}	MAP	73 ± 2	73 ± 3
	HR	58 ± 2	57 ± 3

Values are mean ± SE; n = 15 in each study group.

MAP = mean arterial pressure (mmHg); HR = heart rate (beats/min).

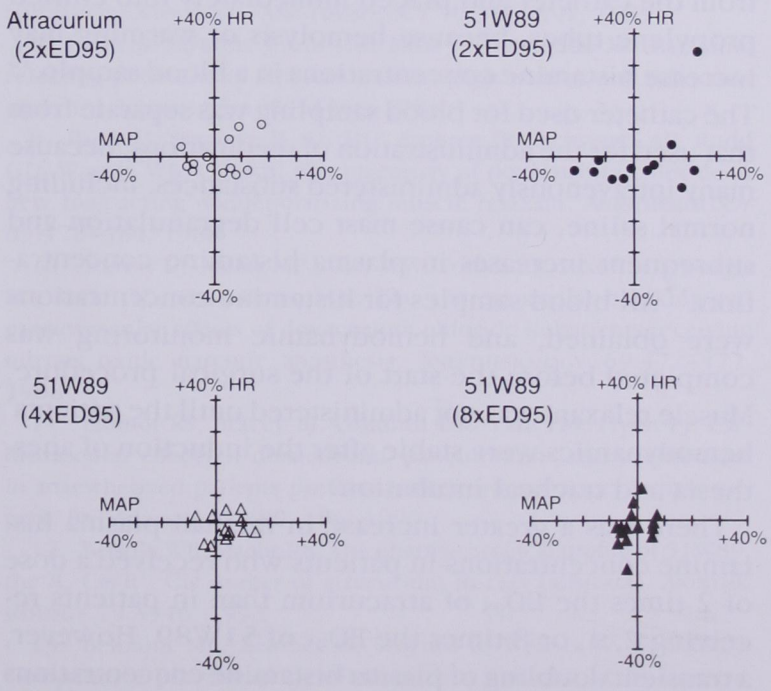

Fig. 2. Maximum heart rate and mean arterial pressure changes during the first 5 min after the administration of the muscle relaxant. Each patient's maximal heart rate and blood pressure changes are graphed as a function of his or her study group, 2 times the ED_{95} of 51W89 or atracurium, 4 times the ED_{95} of 51W89, or 8 times the ED_{95} of 51W89. All measurements were made after intubation and at least 3 min of stable hemodynamic measurements and before surgical stimulation.

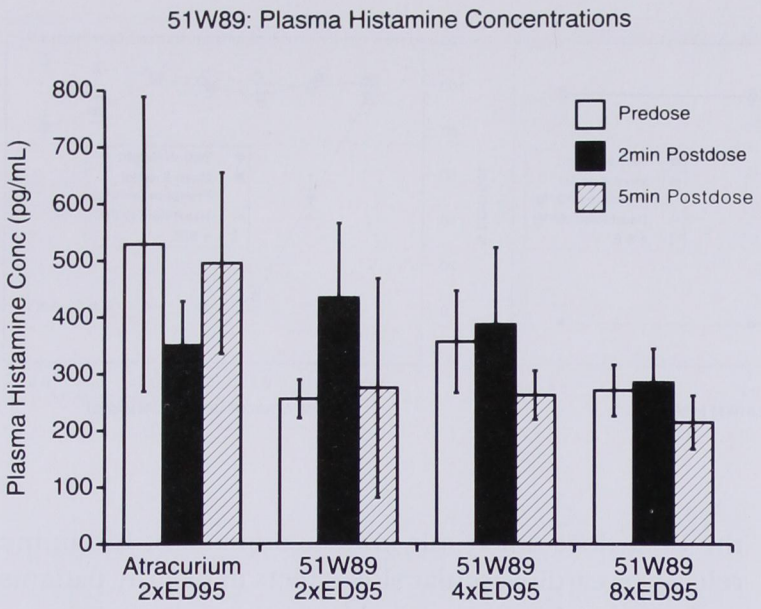

Fig. 3. Mean plasma histamine concentrations in each study group before the administration of relaxant and 2 and 5 min after the administration of relaxant. There were no dose-related changes in plasma histamine concentrations in any of the groups.

tained until at least 10 min after the insertion of the intravenous catheter, and blood was withdrawn gently from the catheter and placed immediately into chilled propylene tubes, because hemolysis or warming may increase histamine concentrations in a blood sample.[16] The catheter used for blood sampling was separate from that used for the administration of medications, because many intravenously administered substances, including normal saline, can cause mast cell degranulation and subsequent increases in plasma histamine concentration.[17] All blood samples for histamine concentrations were obtained, and hemodynamic monitoring was completed before the start of the surgical procedure. Muscle relaxant was not administered until the patients' hemodynamics were stable after the induction of anesthesia and tracheal intubation.

There was a greater increase in median plasma histamine concentrations in patients who received a dose of 2 times the ED_{95} of atracurium than in patients receiving 2, 4, or 8 times the ED_{95} of 51W89. However, a transient doubling of plasma histamine concentrations to values in the range of 1,000–2,000 $pg \cdot ml^{-1}$ was observed in two patients after the administration of a dose of 2 times the ED_{95} and in one patient after a dose of 4 times the ED_{95} of 51W89. Although plasma histamine concentrations of this magnitude may be associated with histamine-like effects, such as facial flushing and transient hypotension and tachycardia,[5,18] none of these three patients exhibited any such clinical signs. Two patients who received atracurium sustained high preinjection values of plasma histamine, and neither of these patients exhibited any clinical evidence of histamine release. Occasional observations of increases in histamine concentrations probably are not drug-related and may be related to other factors associated with anesthesia and surgery.[19] One patient who received atracurium did develop facial flushing. He did not have, however, any increase in his plasma histamine concentration after the administration of the relaxant.

Rapid administration of 51W89 in doses ranging from 2 to 8 times the ED_{95} was not associated with dose-related cardiovascular effects. Effects on mean heart rate and mean arterial pressure in the 5 min after the administration of all doses of 51W89 were minimal and similar to those observed after the administration of 2 times the ED_{95} of atracurium. In earlier studies, hemodynamic changes after the administration of 2 times the ED_{95} of atracurium have been reported, as found in the current study, to be minimal.[5] Rapid administration of doses greater than 2 times the ED_{95} of atracurium (0.6–1.5 $mg \cdot kg^{-1}$) may cause significant but transient decreases in mean arterial pressure and increases in heart rate.[5,20–22] These changes are presumably secondary to the histamine release caused by rapid administration of these large doses of atracurium. The results of the current study suggest that administration of doses of 51W89 up to and including 8 times the ED_{95} is associated with noteworthy hemodynamic stability. The cardiovascular changes observed are not different than after the rapid administration of a dose of atracurium at 2 times the ED_{95}. The cardiovascular effects of rapidly administered doses of atracurium greater than 2 times the ED_{95} were not studied because of ethical concerns regarding their known capacity to liberate histamine.[5,8,20]

It is possible that the anesthetic technique used in this study, that of nitrous oxide, barbiturate, and fentanyl, may have masked the tachycardia associated with histamine release, making it more difficult to recognize one of the clinical signs of this phenomenon. However, hypotension secondary to histamine release should have been more severe than in more lightly anesthetized patients. No patient exhibited a clinically significant decrease in mean arterial pressure. Observed decreases in mean arterial pressure, including the patient whose blood pressure decreased 22%, were gradual

Table 4. Plasma Histamine Concentration (pg/ml) before and after the Administration of Muscle Relaxant

Sample Time	Atracurium	51W89		
	2 × ED_{95}	2 × ED_{95}	4 × ED_{95}	8 × ED_{95}
Baseline	529 ± 260 (131)	255 ± 34 (242)	355 ± 90 (226)	269 ± 45 (217)
2 min postinjection	350 ± 78 (308)	433 ± 132 (173)	385 ± 136 (219)	283 ± 59 (206)
5 min postinjection	495 ± 160 (211)	274 ± 60 (193)	261 ± 43 (220)	213 ± 37 (172)

Values are mean ± SE (with median in parentheses).

and could be attributed to deep anesthesia and lack of surgical stimulation.

In this study, not all patients received the same doses of intravenous anesthetics. Patients receiving 2 times the ED_{95} of 51W89 received significantly more thiopental before the administration of 51W89 than other patients receiving that relaxant. Although demographically there is nothing to make that study group different from the others, there was, as shown in figure 2, relatively more blood pressure and heart rate variability in that group of patients. It also contained two of the three patients who experienced a transient doubling of plasma histamine concentration. As there were no dose-dependent changes in blood pressure, heart rate, or plasma histamine concentrations, it is unlikely that these observations at 2 times the ED_{95} can be attributed to 51W89. The greater variability in blood pressures in patients receiving either 2 times the ED_{95} of atracurium or 51W89 is most likely due to the use of oscillometry rather than direct intraarterial assessment of blood pressure.

In conclusion, 51W89 is a benzylisoquinolinium muscle relaxant with an intermediate duration of action that does not cause histamine release or clinically significant cardiovascular effects at doses up to and including 8 times the ED_{95} for neuromuscular block in patients. Further studies of the pharmacodynamic, hemodynamic, and pharmacokinetic behavior of the compound in special patient populations seem warranted.

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