Title: COMPARISON OF FAST AND SLOW BOLUS INJECTIONS OF MIVACURIUM CHLORIDE UNDER NARCOTIC-NITROUS OXIDE ANESTHESIA

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Introduction. Mivacurium chloride is a new short-acting nondepolarizing bisquaternary ester neuromuscular blocking agent, hydrolyzable by human plasma cholinesterase. Its estimated ED_{95} is 0.09-0.10 mg/kg.[1] The 25-75% recovery index is 5-7 min. While moderate doses of mivacurium have minimal side effects, large doses may cause cardiovascular side effects and cutaneous manifestations which are attributable to histamine release.[2] This study compares the slow vs. fast i.v. injection of large doses of mivacurium chloride to see whether slow injection reduces side effects.

Methods. Eighteen surgical patients with no childbearing potential, aged 20-55, ASA status I-II, with no history of unusual sensitivity to neuromuscular blocking agents, asthma and/or intake of antihistamines within 48 hours of the study consented to the study approved by the Human Subjects Committee. Premedication consisted of meperidine 50-75 mg i.m. and/or diazepam 10 mg p.o. Antihistamines and hydroxyzine were avoided. Narcotic-N_2O anesthesia was induced and maintained with thiopental 4-10 mg/kg, supplemented with droperidol 0-0.1 mg/kg and fentanyl 2-12 μg/kg, or meperidine 2-4 mg/kg i.v. Ventilation was controlled manually before tracheal intubation, followed by the use of a ventilator to deliver 50-70% N_2O in oxygen at 10-15 ml/kg, 10X/min. Core temperature was 35.5-36.5°C. HR, BP and MAP were recorded at one minute intervals. ECG, O_2 saturations and end-tidal CO_2 were continuously monitored. All patients received 0.5-0.7 L. of lactated Ringer's solution or NaCl solution prior to the study. The ulnar nerve was stimulated with supramaximal electric pulses of 0.2 ms at 0.1 Hz. Vital signs and neuromuscular response were stabilized for 5 min. before study began. The first group of 9 patients were given an initial dose of mivacurium 0.25 mg/kg injected i.v. rapidly (5 sec.) as a bolus. The trachea was not intubated until 5 min. later, after 100% neuromuscular block had ensued and cardiovascular responses had been assessed. A second group of 9 patients went through the same procedure except that the 0.25 mg/kg dose of mivacurium was injected slowly over 60-75 sec. In both groups, clinical signs of histamine release and cardiovascular changes, if any, were noted. The onset (beginning of injection to peak effect), magnitude, and duration (beginning of injection to recovery to 25% of control), recovery index (25-75%) of the neuromuscular block were recorded and compared between the two groups. Data were presented as mean ± SEM, $p < 0.05$ being considered statistically significant.

Results. All patients had complete block folowing 0.25 mg/kg of mivacurium. Neuromuscular parameters were not significantly different between the two groups, $p > 0.2$, except that slow injection over 60-75 seconds resulted in a tendency to slow the onset by approximately 1 min., $p = 0.16$.

Neuromuscular Parameters

	Onset (min)	Duration (min)	Recovery Index (min)
Fast Inj.	3.2 ± 0.3	24.2 ± 2.0	8.9 ± 1.3
Slow Inj.	4.1 ± 0.6	24.1 ± 2.3	7.0 ± 0.9

Cardiovascular responses differed significantly between the two groups, $p < 0.05$ by Fisher exact probability test.

Changes in Mean Arterial Pressure

	>25% decrease in MAP	<25% decrease in MAP	Total
Fast Inj.	5	4	9
Slow Inj.	1	8	9
	6	12	18

One patient in the fast injection group had a clinically significant episode of hypotension that required immediate treatment. She stabilized after receiving 1.7 L. of lactated Ringer's solution in 3 min. Other patients required no specific treatments. All patients recovered from hypotension in 3-5 min.

Cutaneous changes also differed significantly between the two groups, $p < 0.05$ by Fisher exact probability test:

	cutaneous flush	no cutaneous flush	Total
Fast Inj.	4	5	9
Slow Inj.	0	9	9
	4	14	18

Cutaneous flush was mild, limited to face, neck, and shoulders. No wheezing or other signs of histamine release were noted.

Discussion. The 0.25 mg/kg dose of mivacurium chloride is the largest bolus dose in our entire project involving a total of 144 patients. It probably borders on or exceeds the advisable clinical dose range for rapid injection. Although most cardiovascular and cutaneous reactions were mild, one patient did have cardiovascular reactions of moderate severity. As is the case in atracurium, slow injection appears to prevent most side effects and markedly increases the margin of safety of mivacurium chloride.

This study was supported in part by Burroughs Wellcome Co.

References.

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