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Mivacurium-induced Neuromuscular Blockade Following Single Bolus Doses and with Continuous Infusion during Either Balanced or Enflurane Anesthesia

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Mivacurium chloride (BW B1090U) was administered to 72 patients during their elective surgery. The eight groups (nine subjects per cell) in the 2 × 2 × 2 study design differed in three factors: the size of the mivacurium bolus dose administered, whether or not this dose was followed by an infusion of mivacurium, and in the technique used for the maintenance of anesthesia. Four groups received a single bolus dose of mivacurium, 0.15 mg/kg, and the remaining four groups received mivacurium, 0.25 mg/kg, administered iv in 15 s. Precisely 2 min later, tracheal intubation was attempted. Conditions were judged to be good or excellent on most occasions, but intubation was not possible for two of the patients in the low-dose and one in the high-dose groups. Four groups, two at each bolus dose, received no additional mivacurium: there was a dose-dependent decrease in the rate of spontaneous recovery following the bolus dose. The other subdivision of groups was the use of either barbiturate–nitrous oxide–narcotic (balanced) anesthesia, or enflurane–nitrous oxide anesthesia; the anesthetic technique did not affect the pattern of spontaneous recovery from either bolus dose. Four groups, again two at each bolus dose, subsequently received an infusion of mivacurium, adjusted to depress the twitch response by approximately 95%. Infusion rates averaged 6.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the groups receiving balanced anesthesia and 4.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for those receiving enflurane anesthesia. Recovery following administration by infusion was slower than that observed following a bolus dose of mivacurium, 0.15 mg/kg but did not differ between the anesthetic groups. Plasma concentrations of mivacurium at the end of the infusion for patients receiving balanced and enflurane anesthesia averaged 227 ng/ml and 173 ng/ml, respectively. (Key words: Anesthetic techniques: balanced; enflurane. Intubation, tracheal. Neuromuscular relaxants: mivacurium.)

MIVACURIUM CHLORIDE (BW B1090U) is a neuromuscular blocking drug with a shorter duration of action than those nondepolarizing agents currently in clinical use.[1–3] If it is assumed that the clinical dose of mivacurium will be at least double its ED_{90}, it is likely to be administered for tracheal intubation in doses of 0.15 mg/kg or more.[1,4–15] A single bolus dose of 0.25 mg/kg has been reported to provide good conditions for intubation in 90–120 s[9]; conditions at 2 min were as good as those obtained 1 min after succinylcholine, 1.0 mg/kg.[5]

When short-acting relaxants are administered by infusion, the clinician can respond rapidly to changing requirements in blockade intensity, either to increase paralysis during surgery or to obtain prompt spontaneous recovery at its end. During balanced anesthesia, spontaneous recovery from an infusion of mivacurium has been reported not to differ from that following bolus doses ranging from 0.1 to 0.3 mg/kg.[1,2] The potentiation of relaxant-induced blockade by inhalation agents, when compared with observations made during balanced anesthesia, is true also for mivacurium. Its bolus dose–response curve is shifted to the left by halothane,[13,15] by enflurane,[7] and by isoflurane[16]; its infusion requirements are reduced in the presence of halothane[17] and of isoflurane.[18]

In this study conditions at intubation were examined in patients precisely 2 min following administration of either 0.15 or 0.25 mg/kg mivacurium. The time-course of recovery from blockade induced by a single bolus dose of mivacurium was recorded during barbiturate–N_2O-narcotic (balanced) or enflurane-N_2O anesthesia; this was compared with the patterns of spontaneous recovery during these anesthetics when mivacurium had been administered by continuous infusion. The study also compared infusion requirements during balanced anesthesia with those obtained during maintenance anesthesia involving enflurane.

Methods

Seventy-two adult patients scheduled for elective surgery gave their institutionally approved written informed consent to enter this study. Three factors are represented in the eight study groups: the size of the mivacurium bolus dose (indicated as A or B), whether or not this was followed by an infusion (1 or 2), and the anesthetic technique used for maintenance (a or b). A randomization table allocated nine patients to each of the eight groups of the 2 × 2 × 2 design.

Anesthesia was induced with thiopental, 3–6 mg/kg iv, and fentanyl, 50–250 mg iv. Immediately following induction of anesthesia, the ulnar nerve was stimulated at the wrist with single supramaximal stimuli of 0.2 ms

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duration every 10 s. A linear force transducer, attached at right angles to the thumb, displayed to a chart recorder. When twitch responses were stable for not less than 3 min, control values were recorded for later calculation of twitch depression, to assess onset, duration, and recovery of blockade.

Mivacurium was administered as a single bolus dose, injected over 15 s into the tubing of a free-flowing iv infusion. The randomization table allotted the 72 patients as (A) 36 to receive mivacurium, 0.15 mg/kg, and (B) 36 patients to receive 0.25 mg/kg. Precisely 2 min later laryngoscopy was begun. Throughout the study, the same laryngoscopist (R.J.F.) attempted and scored conditions at tracheal intubation. The intubation was graded as follows: 1) excellent, no reaction; 2) good, slight cough but jaw and cords well relaxed; 3) poor, cough or movement, cords moderately adducted; and 4) not possible, jaw and/or cords tightly closed.[9] Grades 2–4 were confirmed by an independent second observer.

Anesthesia was maintained with N_2O 66% in O_2; the randomization table allocated patients to receive either (a) additional supplements of thiopental and fentanyl as indicated clinically or (b) enflurane. Enflurane was begun following tracheal intubation, and vaporizer settings were adjusted to maintain end-expired concentrations at 1.26% on a mass spectrometer. Anesthesia continued unchanged throughout recovery from blockade.

No additional mivacurium was administered to 36 patients. In the other 36 patients, a mivacurium infusion was started before intubation, at a rate of 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The infusion rate was adjusted in an attempt to keep twitch depression between 90% and 98%. Two patients were excluded from the postintubation infusion analysis, one because the infusion was later found to have extravasated and the other due to stimulator malfunction. Infusion requirements were compared at the end of the first and last hours of the infusion (within groups, repeated measures), and between groups for the dose and anesthesia factors. The time intervals between 75–25% and 90–10% twitch depression, measured during spontaneous recovery from mivacurium-induced blockade, were examined with three-way analysis of variance, to assess the effects of the size of the bolus dose, the anesthetic technique, and the use of an infusion.

At 30-min intervals during the infusion, 8 ml aliquots of blood were withdrawn rapidly from the basilic vein of the contralateral arm and immediately placed in tubes containing echothiophate. The plasma was separated in a refrigerated centrifuge. Concentrations of mivacurium were later estimated from the deep-frozen plasma. Mivacurium was extracted by solid-phase extraction on a reversed-phase cartridge, which had been preconditioned with methanol and water. Plasma containing 200 ng of doxacurium as an internal standard was then added, followed by 3 ml sequential washes of water, acetonitrile, methanol, and water. Mivacurium and internal standard were then eluted with a 1 ml solution containing 70% methanol and 30% 0.05 M potassium phosphate (*p*H 3). The extracts were analyzed by reverse-phase high performance liquid chromatography (HPLC). A Varian 5060 HPLC was used with a Waters WIP4SP Autosampler, Supelco pre-column, Spherisorb S5C1 column (4.5 mm × 15 cm) and a Spectraflow 757 UV detector set at 210 nm. The mobile phase was 70% acetonitrile and 30% phosphate buffer (*p*H 3) containing 10% methanol. The flow rate was 1.0 ml/min, and the injection volume was 25–100 ml. Data acquisition, peak analysis, and data reduction were performed with a PDP-11/70 minicomputer. The lowest reliable limit of sensitivity is 10 ng/ml. Mivacurium plasma concentrations were estimated for 24 of the 36 infusion patients.

Statistical tests were performed with an SPSS program. Between and within group comparisons of interval data were examined with multivariate analysis of variance. Other tests are as indicated in the related tables. Statistical significance was defined as $P < 0.05$.

TABLE 1. Clinical Characteristics of the Patients, Grouped by Initial Bolus Doses of Mivacurium (mean values ± SD)

	0.15 mg/kg	0.25 mg/kg
Sex (M/F)	21/15	18/18
Age (yr)	45 ± 14	41 ± 14
Height (cm)	171 ± 11	173 ± 10
Weight (kg)	75 ± 13	79 ± 14
Temperature (° C)	35.8 ± 0.5	35.9 ± 0.4

Results

The 72 patients were factored for the single bolus dose of mivacurium; their clinical characteristics appeared to be comparable (table 1). None of the other subdivisions of the study showed between-group differences in their patient characteristics.

Conditions were usually appropriate for intubation 2 min after either dose (table 2). The three patients whose tracheas could not be intubated at the first attempt had not achieved 90% blockade at 2 min, but this was also true of 35 of the 64 patients in whom conditions were graded as either good or excellent. Tracheal intubation in these three patients could be performed when maximal blockade occurred at 4 min.

Table 3 shows the time-course of recovery from mivacurium-induced paralysis for the groups receiving mivacurium only as a single bolus dose. There was a dose-dependent increase in the duration of mivacurium-induced blockade ($P < 0.01$), not differing for the anesthetic technique. The time intervals between 75% and 25%

TABLE 2. Conditions 2 min after a Bolus Dose of Mivacurium: Tracheal Intubation Grades (patient numbers) and Percent Twitch Depression (mean ± SD)

	0.15 mg/kg	0.25 mg/kg
Grade		
Excellent	17	27
Good	13	7
Poor	4	1
Not possible	2	1
Total	36	36
Twitch depression (%)	76 ± 20	90 ± 15

The contingency coefficient was not significant for the two doses. The intensities of twitch depression differed ($P < 0.001$, Mann-Whitney).

twitch depression and between 90% and 10% twitch depression (table 4) were also dose-dependent ($P < 0.01$).

The results obtained during mivacurium infusion are shown in table 5. Neither the infusion rates nor the plasma concentrations obtained at the end of the first hour were found to differ from those at the end of the infusion. By the end of the infusion, the mean infusion rate for patients anesthetized with enflurane was 30% less than that for patients anesthetized with balanced anesthesia ($P < 0.05$). This difference was also reflected in the associated plasma concentrations of mivacurium, although this was measured in only 24 of the 36 patients.

Following cessation of the infusion, twitch response in the group receiving balanced anesthesia returned to 25% of control in 6.6 ± 2.0 min, and 8.1 ± 3.1 min in the enflurane group. The anesthetic techniques appeared not to affect the postinfusion time intervals, either between 75–25% blockade or between 90–10% blockade (table 4). Following the infusion, these indices of recovery did not differ from those found with bolus administration of 0.25 mg/kg, although those associated with 0.15 mg/kg were significantly shorter ($P < 0.02$). Using pooled data, the correlation coefficient between the infusion rate and the 75–25% recovery index was $r = 0.55$.

TABLE 3. Recovery of Twitch Depression Following a Single Dose of Mivacurium: Intervals Required for Spontaneous Return (in minutes) from the Time of Administration of the Bolus Dose

	0.15 mg/kg		0.25 mg/kg	
Anesthesia	Balanced	Enflurane	Balanced	Enflurane
90%	12 ± 2	12 ± 4	20 ± 6	18 ± 5
75%	14 ± 3	14 ± 4	23 ± 7	21 ± 5
25%	20 ± 4	20 ± 6	32 ± 11	29 ± 7
5%	25 ± 8	24 ± 8	40 ± 16	35 ± 9

Two-way analysis of variance indicated that all four time intervals show statistically significant dose-dependency, not differing for anesthetic technique.

TABLE 4. Mean Time Intervals (±SD) during Recovery (minutes)

	Balanced	Enflurane
Times between 75% and 25% twitch depression		
Following a single bolus dose		
Groups A1a and A1b, mivacurium, 0.15 mg/kg	5.7 ± 1.8	5.9 ± 2.0
Groups B1a and B1b, mivacurium, 0.25 mg/kg	8.4 ± 4.0	8.1 ± 2.2
Bolus plus infusion		
Groups A2a and A2b	9.9 ± 6.7	9.8 ± 3.6
Groups B2a and B2b	9.1 ± 4.3	9.4 ± 4.6
Between 90% and 10% depression		
Single bolus		
Groups A1a and A1b	10.8 ± 5.1	11.0 ± 3.9
Groups B1a and B1b	16.4 ± 8.0	14.4 ± 3.8
Bolus plus infusion		
Groups A2a and A2b	17.1 ± 7.1	18.3 ± 5.0
Groups B2a and B2b	18.7 ± 9.7	20.2 ± 12.8

Multivariate analysis of variance indicated that those time intervals for mivacurium 0.15 mg/kg differed from those for a bolus dose of mivacurium 0.25 mg/kg and for the infusion groups. Intervals were not found to differ between anesthetic techniques.

Discussion

This study differs from the first major review of mivacurium pharmacology[1] in finding a dose-dependent decrease in the rate of recovery from mivacurium-induced blockade (tables 3 and 4). The durations described for either single dose[1,3,16] resemble those in table 3. The 25–75% recovery index for a bolus dose of 0.15 mg/kg was similar to the 5.5–9.5 min reported elsewhere.[1,10,14,18] The recovery index for a single dose of mivacurium, 0.25 mg/kg, also fell in the range of means of 6.6–8.9 min reported for adults.[1,10] Spontaneous recovery following the infusion was slower than found by other workers: the mean 9.5 min between 75% and 25% paralysis in table 4 was longer than the 6–8 min reported elsewhere.[1,8,18] The postinfusion interval between 90% and 10% paralysis is also greater.[3] These differences are unlikely to be of importance clinically.

Assuming these differences in duration of effect to be real, the quicker recovery from the bolus dose of 0.15 mg/kg may be related to redistribution enabling a more rapid decline in mivacurium plasma concentrations. With higher dosage or infusion, it is more likely that the slower elimination phase affected blockade, prolonging the time during which plasma mivacurium concentrations remained in the range related to clinical paralysis.[19] Even without this pharmacokinetic hypothesis, the findings in tables 3 and 4 do not support the concept that mivacurium lacks the "pharmacodynamic cumulation" seen with single bolus doses.[1]

TABLE 5. Results Observed During Mivacurium Infusion, Mean (±SD)

	0.15 mg/kg		0.25 mg/kg	
	Balanced	Enflurane	Balanced	Enflurane
End of 1 h				
Number of patients	9	8	9	8
Paralysis (%)	92 ± 5	96 ± 3	93 ± 3	95 ± 2
Infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	6.7 ± 2.6	4.6 ± 1.9	5.2 ± 1.6	4.2 ± 1.0
Mivacurium concentration (ng/ml)	229 ± 73	171 ± 33	200 ± 68	162 ± 44
End of infusion				
Duration (min)	122 ± 14	116 ± 34	132 ± 25	113 ± 16
Paralysis (%)	95 ± 2	95 ± 2	94 ± 1	96 ± 1
Infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	6.8 ± 2.5	4.6 ± 2.1	5.3 ± 1.8	3.8 ± 1.4
Mivacurium concentration (ng/ml)	239 ± 81	167 ± 42	203 ± 76	167 ± 51

Multivariate analysis of variance indicated that the infusion requirements and plasma concentrations of mivacurium differed significantly for the anesthetic technique but not across time (repeated measures), nor with size of the initial bolus dose.

The infusion requirements shown in table 5 are similar to those reported previously during balanced anesthesia for adults in which infusion rates averaged between 4.8 and 8.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[2,8,18,20,21] During anesthesia with isoflurane the rate was reduced from 7.6 to 4.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[18] The slower recovery of patients whose infusion requirements were lower than average suggests that the clinician should be prepared to discontinue their mivacurium infusion earlier than in patients who are less sensitive. In children mivacurium infusion requirements were greater during balanced anesthesia than with N_2O–halothane anesthesia, averaging 16 and 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively[17]; these values indicate that rates of mivacurium infusion suitable for adults will be inadequate for children. In a similar study, the infusion rates of 14.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with N_2O–narcotic and 11.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with N_2O–halothane were associated with plasma concentrations of 0.26 $\mu g/ml$ and 0.23 $\mu g/ml$, respectively.[22]

This study does confirm the findings of other groups investigating the adequacy of relaxation provided by mivacurium as a single bolus dose two or three times greater than its ED_{95}.[1–15] It provided good or excellent conditions for intubation at 2 min in most of the patients. Yet, because there was a minority in whom conditions were inadequate at 2 min,[11] we are reluctant to advocate its preference over succinylcholine when rapid tracheal intubation is desirable.

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