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Pharmacodynamic and Hemodynamic Effects of Mivacurium in Infants Anesthetized with Halothane and Nitrous Oxide

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Background: **The newly developed neuromuscular blocking agent, mivacurium, has been evaluated in adults and children, but there are no data on its effects in infants. This study was designed to evaluate the neuromuscular effects of mivacurium by dose-response analysis, and its cardiovascular effects in 90 infants 2–11 months of age anesthetized with 1% halothane and nitrous oxide:oxygen.**

Methods: **The neuromuscular response was measured by recording the force of contraction of the adductor pollicis during train-of-four stimulation at 0.1 Hz. The infants were divided according to age into two equal groups of 45; group A infants were 2–6 months of age, and group B infants were 7–11 months of age. Each group was further subdivided into five subgroups of nine. Infants in group A received mivacurium at sequential doses of 40, 50, 55, 75, and 150 μg/kg, while those in group B received mivacurium at doses 40, 50, 60, 75, and 150 μg/kg. The first four doses in each group were used to determine dose-response relationships. The last two doses of 75 and 150 μg/kg were based on the observed preceding dose-response data to approximate the ED_{95} and $2XED_{95}$. Heart rate and blood pressure were determined every minute for a minimum of 3 min after mivacurium.**

Results: **The effective doses for 50% depression of the first twitch response of the train-of-four (ED_{50}) were 44–50 μg/kg (confidence limits 29–74 μg/kg), without any significant difference between groups A and B. In both groups, a larger dose of mivacurium, 150 μg/kg, caused complete ablation of the twitch response in 1.3 ± 0.2 min (mean ± SE) with recovery to 5, 25, and 95% of control in 7.6 ± 0.5, 9.4 ± 0.6, and 16.2 ± 0.9 min, respectively. In infants, the 25–75% recovery index was 3.8 ± 0.4 min, and the 5–95% recovery index was 8.5 ± 0.8 min. In 28 infants, in whom surgical relaxation was required for more than 20 min, the infusion requirements to maintain 90–99% neuromuscular block in infants 2–6 and 7–11 months of age were 12.1 ± 1 and 9.9 ± 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively (NS). No significant changes of heart rate or blood pressure occurred in infants, except in the subgroup of infants 7–11 months of age who received 150 μg/kg mivacurium. In this group, a 13-mmHg increase in mean systolic blood pressure was seen without any significant change in diastolic pressure or heart rate. In addition, in 7 of 36 patients receiving 75–150 μg/kg mivacurium, a greater than 29% change in systolic or diastolic pressure occurred. One infant with cholinesterase deficiency had a prolonged neuromuscular block from mivacurium.**

Conclusions: **The ED_{50} duration of action and infusion requirements of mivacurium in infants 2–6 months of age are comparable with those of infants 7–11 months of age. (Key words: Anesthesia, pediatric: infants. Neuromuscular relaxants: mivacurium.)**

MIVACURIUM chloride is a new synthetic bis-benzylisoquinolinium nondepolarizing neuromuscular blocking agent. Its short duration of action is caused by hydrolysis by plasma cholinesterase. Previous studies in adults and children have demonstrated its safety and efficacy.[1–8] Children have been shown to require larger doses of mivacurium, and to recover faster, than adults.[1–8] Because infants often respond differently to the effects of a relaxant than do children or adults,[9–13] the current study was designed to study the neuromuscular and cardiovascular effects of mivacurium in 2–11-month-old infants.

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Materials and Methods

The protocol was approved by the Subcommittee on Human Studies of the Committee on Research, and by the Pharmacy Committee of Massachusetts General Hospital. Written informed consent was obtained from a parent or guardian for each patient.

Ninety infants (ASA physical status 1–2) requiring tracheal intubation and neuromuscular relaxation for elective surgical procedures were studied. None of the infants were receiving aminoglycoside antibiotics or antihistaminics 24 h before surgery. When appropriate (primarily in infants 10–11 months of age), patients were premedicated with rectal methohexital 25–30 mg/kg.

Infants were assigned to two major groups (A and B) according to age. Group A infants were 2–6 months of age, and group B infants were 7–11 months of age. In all subjects, anesthesia was induced with halothane and nitrous oxide:oxygen, and maintained at 1% end-expired halothane concentration and nitrous oxide/oxygen. The electrocardiogram, oscillometric blood pressure (Dinamap, Tampa, FL), precordial/esophageal heart sounds, hemoglobin oxygen saturation, end-expired carbon dioxide, and esophageal temperature were monitored. Whenever possible, a venous blood sample was drawn for determination of plasma cholinesterase and dibucaine number.

The ulnar nerve was stimulated at the wrist *via* surface electrodes. Supramaximal train-of-four stimuli (2 Hz for 2 s) were generated by a Grass S44 (Quincy, MA) stimulator at a rate of 0.1 Hz. The response of the adductor pollicis was recorded *via* a Grass FT-03 force displacement transducer. When blood pressure, heart rate, and neuromuscular response to ulnar nerve stimulation were stable for 2 min, mivacurium was administered as a rapid intravenous bolus dose.

Patients of the two main groups were studied sequentially as five subgroups of nine. Subgroups in group A received mivacurium at doses of 40, 50, 60, 75, and 150 μg/kg, respectively, and subgroups in group B received doses of 40, 55, 60, 75, and 150 μg/kg, respectively. In each major group, the data from the previous subgroups were used to project the dose for the next higher dose. The larger two doses approximated the ED_{95} and $2 \times ED_{95}$, as determined from the dose-response analysis of the first three groups.

Heart rate and blood pressure were recorded before mivacurium and at 1-min intervals for 3 min immediately after the initial dose. Neither intubation nor surgical stimuli occurred during this time. If the observed neuromuscular block was less than 95% of control, an additional dose of 100 μg/kg was administered, and tracheal intubation was performed.

If the surgical procedure warranted it, a continuous infusion of mivacurium was started after spontaneous recovery of the twitch response to more than 25% of control. For infusion, mivacurium was diluted to 500 μg/ml and administered *via* a controlled infusion pump (Baxter AS20S, Round Lake, IL). The infusion rate was initially set at 14 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and, thereafter, was adjusted to provide a twitch depression of 90–99% of the control twitch response.

All patients were allowed to recover spontaneously from mivacurium-induced neuromuscular block to at least 25% of twitch response. Thereafter, spontaneous recovery was evaluated in odd-numbered patients, and pharmacologic reversal with 20 μg/kg neostigmine and 10 μg/kg atropine was evaluated in even-numbered patients. Clinical evidence of neuromuscular recovery was also assessed at the end of surgery and approximately 1 h later in the recovery room. Signs of adequate recovery included effortless opening of the eyes, holding up or moving the head, lifting up the legs, crying, and adequate sucking.

The time to maximum depression of the twitch response (onset time) was determined by measuring the time from the initial administration of mivacurium to the onset of maximum block. Twitch depression was expressed as the percent reduction of the first twitch of the train-of-four (T_1) relative to control. Recovery to 5, 25, 50, 75,and 95% of control was also evaluated.

The dose-response data for neuromuscular blockade from the first four subgroups of patients were analyzed by two statistical models. In the first model, linear regression of the probit values corresponding to the percentage of neuromuscular block was used. In the linear regression analysis, the method of Litchfield and Wilcoxon was used, as well as testing for the parallelism of the dose-response curves. The second model consisted of nonlinear dose-response analysis using the Hill equation (E-Max model). Other appropriate comparisons were made by linear regression, Student's *t* test, or ANOVA. Mean and SE were calculated by standard formulae. Data are presented as mean ± SE, unless otherwise indicated. Data were considered significant when $P < 0.05$.

Table 1. The Calculated Effective Doses of Mivacurium in Infants Anesthetized with N_2O:O_2 Halothane

Effective Dose (μg/kg)	Probit Log Dose Model		E_{max} Nonlinear Model	
	2–6 Months	7–11 Months	2–6 Months	7–11 Months
ED_{25}	39	41	35	38
ED_{50}	45	50	44	49
ED_{75}	53	54	56	62
ED_{95}	65	66	83	94

ED = effective dose (resulting in percent twitch depression).

Results

The mean age (± SD) of the infants studied in group A was 4.6 ± 1.3 months (range 2.5–6.9 months), and the mean weight of infants in this group was 7.1 ± 1.3 kg (range 4.5–10 kg). Group B infants had a mean age of 9.3 ± 1.6 months (range 6.1–11.7 months), and a mean weight of 9.4 ± 1.4 kg (range 5.2–13 kg).

Neuromuscular Effects

The effective doses determined from the dose-response relationships from the first four subgroups in each group are summarized in table 1. The ED_{50}, as determined with the linear and nonlinear response analyses, was comparable at 44–50 μg/kg. The 95% confidence limits of ED_{50} were 29–72 μg/kg for group A and 30–74 μg/kg for group B. The correlation coefficients between probit and log doses were highly significant (group A, r = 0.71; group B, r = 0.72, $P < 0.0001$). The estimate for the slope of the log dose (Betal) was 10.6 for group A and 11 for group B ($P < 0.0001$). The ED_{95} calculated from the nonlinear model (group A, 83 μg/kg; group B, 94 μg/kg) were higher than those calculated from the probit-log dose analysis (group A, 65 μg/kg; group B, 66 μg/kg).

In infants receiving 75 μg/kg mivacurium, maximum suppression of the twitch response occurred in 2.8 ± 0.3 min, and recovery of T_1 to 25 and 95% of control took 7.2 ± 0.8 and 14.1 ± 1.2 min, respectively (table 2). There were no significant differences in the recovery parameters between these two groups of infants, except in the 95% recovery rate ($P < 0.05$; table 2). Administration of 150 μg/kg mivacurium produced complete suppression of the twitch response in all infants. Time to onset after 150 μg/kg was 1.3 ± 0.2 min, a significantly shorter ($P < 0.01$) time than that for 75 μg/kg. Recovery to 25%, however, was prolonged by only 1–2 min; the infants in these latter subgroups recovered to 25 and 95% of control twitch height in 9.4 ± 0.6 and 16.2 ± 0.9 min, respectively. In the infants in whom spontaneous recovery occurred, 25–75% recovery occurred in 3.8 ± 0.4 min, and 5–95% recovery occurred in 8.5 ± 0.8 min. There were no significant differences in the recovery indices of the two main groups of infants.

Cardiovascular Effects

In measurements taken in the absence of surgical stimulation or tracheal intubation, mivacurium did not cause any appreciable changes in the mean or diastolic blood pressures, or the heart rate, in the ten subgroups of infants studied. The only significant change noted was a 13% increase in mean systolic blood pressure in infants 7–11 months of age who received 150 μg/kg

Table 2. The Neuromuscular Effects of 75 and 150 μg/kg Mivacurium in Infants Anesthetized with N_2O:O_2 Halothane

Group	Mivacurium Dose (μg/kg)	Maximum Block (% T_1/Control)	Time from Injection to Maximum Block (min)	Recovery of T_1/Control (min)			Recovery Index (min) (25–75%)	Clinical Recovery (min) (5–95%)
				5%	25%	95%		
2–6 months (n = 8)	75	97.5 ± 1.3 (90–100)	2.3 ± 0.2 (1.7–3)	5 ± 0.6 (4–7)	6 ± 0.5 (5–9)	11.7 ± 1.1* (8–16)	3.2 ± 0.3 (2–4)	7.5 ± 0.1 (6–9)
7–11 months (n = 9)	75	93.8 ± 5.1 (53–100)	3.1 ± 0.2 (2–4)	6.6 ± 1 (3–11)	8.8 ± 1 (5–13)	17.5 ± 1.6* (14–23)	4.6 ± 0.6 (2.5–7)	9.8 ± 1.5 (5–14)
2–6 months (n = 9)	150	100	1.3 ± 0.2 (0.7–2.2)	7.9 ± 0.8 (5–12)	9.7 ± 0.9 (7–15)	16.5 ± 1.3 (12.5–23)	3.5 ± 0.4 (2–5)	8.2 ± 0.6 (7–11)
7–11 months (n = 9)	150	100	1.4 ± 0.2 (1–2.4)	7.4 ± 0.5 (5–10)	9.2 ± 0.5 (7–12)	15.6 ± 0.7 (14–18)	4 ± 0.2 (3.5–4.5)	8.5 ± 0.6 (7–10.5)

Data are means ± SE; ranges are given in parentheses.

* $P < 0.05$ between subgroups receiving 75 μg/kg mivacurium.

mivacurium (table 3). In addition, however, more than a 29% change in systolic or diastolic pressure occurred in 7 of the 36 patients receiving 75–150 μg/kg mivacurium (fig. 1). The reflection of these separate measurements on the mean blood pressure was less frequent. Only two of these seven patients had a >29% change in mean blood pressure; in one, it increased 34%, and in the other, it decreased 30%.

Infusion Requirements

In 60 infants, an infusion of mivacurium was started when the twitch response had recovered to a mean that was 54 ± 8% of control. The mean duration of infusion was 68 ± 13 min. Because frequent adjustments in the infusion rate were needed in the first 15 min to maintain neuromuscular block in the desired range (90–99%), data were not analyzed in this interval. In 28 patients, the infusion period studied lasted for more than 18 min; in these patients, the mean duration of infusion was 78 ± 15 min (range 33–230 min), and the requirement was 12.1 ± 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in group A (n = 16) and 9.4 ± 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in group B (n = 12) mivacurium. The difference between the two groups was not statistically significant. There was a wide individual variation in the infusion rates, with the rates varying from 3 to 24 $\mu g \cdot kg^{-1} \cdot min^{-1}$. For the patients who received mivacurium infusions, the mean twitch depression at the time of discontinuation was 94.6 ± 1.6%. Recovery to 25 and 95% occurred in 2.8 ± 0.3 and 8.4 ± 0.5 min, respectively. The 25–75% recovery index was 3.3 ± 0.2 min, and 5–95% recovery was 8.4 ± 0.5 min. These values approximate those recorded after the initial bolus doses of 75 or 150 μg/kg mivacurium.

Reversal of Neuromuscular Effects

In 31 patients, the neuromuscular effects of mivacurium were antagonized by neostigmine 20 μg/kg and atropine 10 μg/kg when the recovery of T_1 was 33 ± 4% of control; in these patients, T_1 returned to 75% of control in 2.5 ± 0.4 min and to 95% in 4 ± 0.4 min. None of the patients (neither those in whom reversal was attempted nor those in whom recovery occurred spontaneously) showed any clinical evidence of neuromuscular weakness at the completion of surgery or in the recovery room approximately 1 h later.

Relation with Plasma Cholinesterase

The mean plasma cholinesterase value of the infants in group A was 2.9 ± 0.5 (range 2.6–4.1 U/ml) units, and the dibucaine number was 86.9 ± 3.1% (range 79–89%). In group B infants, these values were 3 ± 0.6 U/ml (1.8–4.2) and 87.3 ± 1.6% (range 86–89). The normal range for plasma cholinesterase activity in the laboratory is 1–3.5 U/ml, and the dibucaine number is 70–90%. No correlation was noted between plasma cholinesterase or dibucaine number and the infusion requirements.

In one infant with markedly low enzyme activity (plasma cholinesterase 0.5 U/ml; dibucaine number 40%), the effect of 75 μg/kg mivacurium was greatly prolonged. Forty-five minutes after the initial mivacurium dose, weak diaphragmatic movements were noted; atropine and neostigmine were given, first as a test dose, followed by additional doses totalling 70 μg/kg and 140 μg/kg, respectively, with adequate neuromuscular recovery. The data from this infant were excluded in the analysis of recovery times.

Table 3. Maximal Systolic/Diastolic Pressures and Heart Rates in Infants during the First 3 min after 75 and 150 μg/kg Mivacurium during N_2O:O_2 Halothane

Mivacurium Dose (μg/kg)	Blood Pressure (mmHg)		Heart Rate (beats/min)	
	Preinjection	Postinjection	Preinjection	Postinjection
75 (2–6 months)	71 ± 4 / 37 ± 2	75 ± 4 / 38 ± 2	115 ± 5	116 ± 5
150 (2–6 months)	79 ± 3 / 39 ± 2	81 ± 4 / 41 ± 3	125 ± 5	123 ± 6
75 (7–11 months)	81 ± 5 / 45 ± 5	82 ± 4 / 39 ± 4	121 ± 4	121 ± 5
150 (7–11 months)	80 ± 5* / 46 ± 3	93 ± 8* / 53 ± 5	119 ± 4	127 ± 4

Data are means ± SE.

* $P < 0.05$.

Discussion

Previous studies have demonstrated that mivacurium can be safely used in children and adults;[1–8] the current study shows that mivacurium can also be used effectively in infants aged 2–11 months. In our institution, we previously conducted dose-response analyses with mivacurium in children 2–12 yr of age.[1] In that study, using the same technique as described above and linear regression analysis, we found the ED_{50} and ED_{95} to be 51 and 95 μg/kg, respectively (in children with halothane). The comparable doses for infants are 47 and

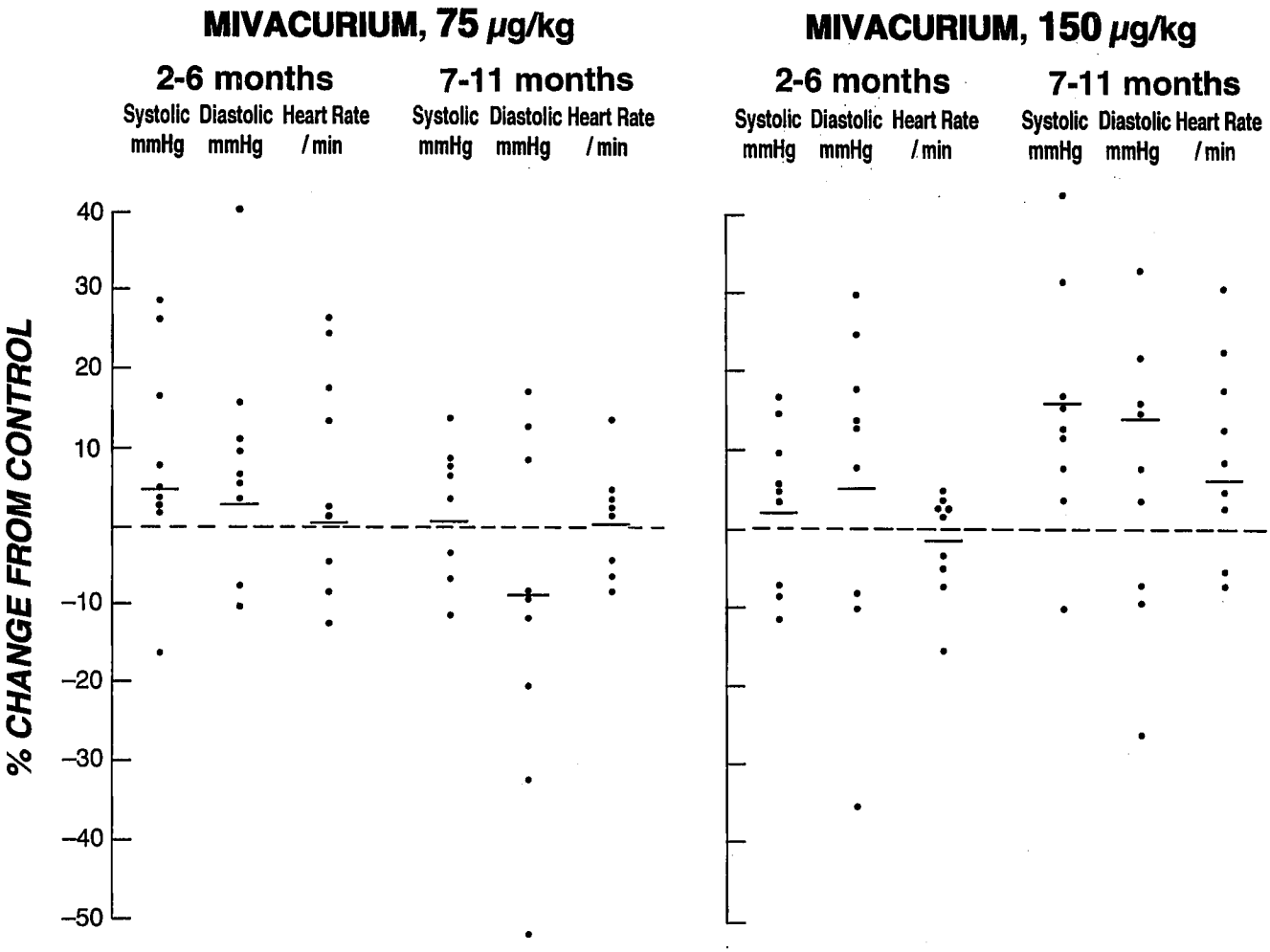

Fig. 1. The percent maximal changes of systolic/diastolic pressures and heart rate in infants after 75 and 150 μg/kg mivacurium during nitrous oxide:oxygen halothane anesthesia.

65 μg/kg. The lower doses compare well with those identified by investigators at another institution using the electromyogram in children. In that study, the ED_{50} and ED_{95} were reported to be 52 and 89 μg/kg, respectively.[2] Infants also show a decreased dose requirement when compared with adults. The ED_{95} doses in infants are generally less than those in adults. Studies using an nitrous oxide/oxygen opioid technique (linear regression analysis) report the ED_{95} in adults to be 73–81 μg/kg,[3,14,15] and, with halothane, to be 81 μg/kg.[5]

In comparing the onset time of 200 μg/kg mivacurium in children with that of 150 μg/kg in infants, we note that the onset times in children (1.6–1.9 min) are similar to infants (1.4–1.7 min). However, the maximum block was slower in onset in adults than in infants or children. In adults, the reported onset time with 150 μg/kg ($2 \times ED_{95}$) has been 2.8–3.8 min,[5,8,14] more than twice that in infants. These data agree with previous observations that onset of action occurs more quickly in infants and children than in adolescents or adults.[15,16]

When comparing the recovery of the twitch response from comparable ED_{95} doses of mivacurium in infants (75 μg/kg) and children (90 μg/kg), we note similar recovery times (about 15 min to 95% recovery in both cases). The same is noted when the effect of a 150-μg/kg dose in infants is compared with a comparable dose of 200 μg/kg in children; here, we note 7.4 min to 5% recovery in infants and 8.5 min in children.[1] The 25–75 and 5–95% recovery indices are also similar in in-

fants and children, about 4 and 9 min. When the recovery times for mivacurium are compared with atracurium and vecuronium, we noted that infants recovered three times faster from mivacurium than from atracurium or vecuronium.[17,**] In this study, the 25–75% recovery is about 4 min for mivacurium, whereas, with atracurium and vecuronium, it is about 12 min.[17,**]

A study in adults using a dose of 150 μg/kg mivacurium during halothane anesthesia (single twitch 0.1 Hz) indicated recovery of twitch height from injection to 25 and 95% to be 19 ± 1 and 30 ± 1 min, respectively.[5] The current study in infants shows the comparable values to be only 9.4 ± 0.6 and 16.2 ± 0.9 min, respectively. The standard recovery indices demonstrate the same faster tendency; in infants, recovery from 25–75 and 5–95% are 3.8 ± 0.4 and 8.5 ± 0.8 min, respectively, whereas, in adults, recovery from 25–75 and 5–95% are about 7–9 and 13–14 min, respectively.[19]

The mean infusion requirement to maintain 90–99% depression of the twitch response was 10.9 ± 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This requirement is comparable with those previously reported in children (10.4 ± 0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 12.4 ± 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[6,4] However, there is wide individual variation in all groups of patients (*i.e.*, infants, children, and adults), with individual dosages varying between 2–24 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[18,19] Our observation of similar infusion requirements in infants and children is markedly different than that of adults. In adults, the reported values are 6.7–8.3 $\mu g \cdot kg^{-1} min^{-1}$ [14,19] (nitrous oxide/oxygen opioid anesthesia). This difference cannot be explained by plasma cholinesterase differences. The relatively larger blood volume of pediatric patients (ml/kg), their clearance, and the sensitivity of the myoneuronal junction may all contribute to various degrees.

In this study, with doses up to 150 μg/kg, no significant change in pulse rate or blood pressure was noted, except for the slight increase in the systolic blood pressure after 150 μg/kg mivacurium in infants 7–11 months of age. No generalized flushing or rashes were observed. It is interesting to note that no cardiovascular changes have been observed in children with doses up to 200 μg/kg.[1,2] In adults, however, doses in the range of 200–250 μg/kg have sometimes resulted in transient decreases in blood pressure and a small concomitant rise (6%) in pulse rate; these effects were generally associated with flushing of the skin and an increase in plasma histamine levels.[20]

Several instances of >29% change in systolic or diastolic pressure were noted after the larger doses of mivacurium in infants. Frequently, these changes occurred in only one of the parameters (systolic or diastolic), and hence the effect on the mean blood pressure was less apparent. They were not associated with changes in the heart rate. These changes were transient. With tracheal intubation, all the infants demonstrated an increase in heart rate and blood pressure.

In conclusion, mivacurium in infants, as in children and adults, is a short-acting neuromuscular blocking agent. Doses up to 150 μg/kg ($2 \times ED_{95}$) are well tolerated in infants. The ED_{50} doses of mivacurium in infants are comparable with those previously reported in children.

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