The neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) were evaluated in 96 children (2–12 yr) during N₂O∶O₂, halothane or N₂O∶O₂ narcotic anesthesia. Neuromuscular response was evaluated by recording the force of contraction of the adductor of the thumb during train-of-four stimulation at 0.1 Hz. The children were divided into two groups. Patients in group A (n = 45) were anesthetized with N₂O∶O₂ and halothane (1% inspired) and patients in group B (n = 45) were anesthetized with N₂O∶O₂ and fentanyl or morphine. Each group was further divided into five subgroups of nine children. Children in the first three sets of subgroups (A₁–A₅, B₁–B₅) received an initial dose of 0.02, 0.04, 0.05, 0.06 or 0.07 mg/kg mivacurium to determine dose response relationships under the different anesthetic regimens. The ED₉₀ and ED₉₅ neuromuscular blocking doses calculated from this single dose technique were 0.051 mg/kg and 0.095 mg/kg, respectively, in children anesthetized with halothane N₂O∶O₂, and 0.059 mg/kg and 0.11 mg/kg in children anesthetized with N₂O∶O₂ narcotic. The fourth subset of each group (A₆ and B₆) received 0.09 mg/kg and 0.11 mg/kg mivacurium, the estimated ED₉₀ for each respectively. The last subset (A₇ and B₇) received 0.2 mg/kg. This dose induced 100% depression of the twitch response in all 18 patients in 1.8 ± 0.1 min, with recovery to 5%, 25%, and 95% of control occurring in 8.4 ± 0.5, 11.2 ± 0.6 and 18.4 ± 1.6 min, respectively. The recovery indices for all patients were 4.5 ± 0.6 min for 25–75% recovery and 9.7 ± 2.2 min for 5–95% recovery. In 17 patients the neuromuscular effects of mivacurium were satisfactorily antagonized by atropine 0.03 mg/kg and edrophonium 0.5 mg/kg. Furthermore, no clinically or statistically significant change in heart rate or blood pressure occurred following the administration of mivacurium. Mivacurium is a short-acting, nondepolarizing neuromuscular blocking agent that can be safely used in children. (Key words: Anesthesia; pediatric. Blood pressure; drug effects. Enzyme: plasma cholinesterase. Monitoring: train-of-four. Neuromuscular relaxant: mivacurium chloride.)

MIVACURIUM CHLORIDE (BW B1090U) is a new synthetic bis-benzyloquinolinium nondepolarizing neuro-

muscular blocking agent with a short duration of action. In vitro it has been found to undergo hydrolysis by human plasma cholinesterase.¹

Initial adult human studies have shown mivacurium to be devoid of toxicity.²⁻⁷ The present study was undertaken to study the neuromuscular and cardiovascular effects of mivacurium in children.

**Methods**

The protocol was approved by the Subcommittee on Human Studies, Committee on Research, and by the Pharmacy Committee of the Massachusetts General Hospital. Parental or guardian written informed consent was obtained for each patient and also from children 7 yr of age and older.

Ninety children (ASA physical status 1 or 2) requiring tracheal intubation and/or neuromuscular relaxation for elective surgical procedures were studied. None of the children were receiving aminoglycoside antibiotics or antihistamines 48 h prior to surgery; none received anticholinergic medications prior to the administration of mivacurium. Premedication consisted of rectal methohexital (25–30 mg/kg) in children younger than 8 yr of age. Older children were not premedicated. The children were divided into two groups (A & B) according to the anesthetic technique. In group A (n = 45) anesthesia was induced with nitrous oxide and oxygen followed by halothane up to 4%; subsequently the concentration was decreased and maintained at 1% (inspired). In group B (n = 45) anesthesia was induced with thiopental (5–7 mg/kg IV) followed by nitrous oxide and oxygen in a 2:1 ratio in combination with fentanyl 1–2 μg/kg or morphine 0.1 mg/kg in increments. The electrocardiogram, oscillometric blood pressure (Dinamap®), precordial/esophageal heart sounds, O₂ saturation, end-expired CO₂, and esophageal temperature were monitored. The end-expired CO₂ was maintained at 34–45 mmHg and the temperature above 35.5°C. A venous blood sample was drawn for 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 S88 stimulator at a rate of 0.1 Hz. The response of the adductor of the thumb was recorded via a Grass FT-03 force displacement transducer on a polygraph. When blood pressure, heart rate, and neuromuscular response to ulnar nerve stimulation...
were stable for at least 2 min, mivacurium was administered as a rapid iv bolus.

Each of the two main groups of patients was studied in five subgroups of nine according to the following mivacurium dosing schedule. Group A (halothane anesthesia):

A1: Based on initial adult studies this group was scheduled to receive 0.02 mg/kg mivacurium; in the first three patients, however, this dose resulted in <1% twitch depression. Consequently, the six remaining patients were given 0.04 mg/kg of mivacurium.

A2: 0.05 mg/kg.
A3: 0.06 mg/kg.
A4: 0.09 mg/kg, the ED$_{95}$ dose estimated from subgroups A1–A3.
A5: 0.2 mg/kg, approximately twice the ED$_{95}$ dose.

Group B ($N_2O$:O$_2$ narcotic anesthesia).

These subgroups received mivacurium as follows:

B1: 0.05 mg/kg.
B2: 0.06 mg/kg.
B3: 0.07 mg/kg.
B4: 0.11 mg/kg, the ED$_{95}$ dose estimated from subgroups B1–B3.
B5: 0.2 mg/kg, approximately twice the ED$_{95}$ dose.

Patients in subgroups A1–A3 and B1–B3 were administered an additional 0.1 mg/kg dose of mivacurium 5 min after the initial mivacurium dose. In these patients, as well as in patients in subgroups A4, A5, B4, and B5, supplemental doses of mivacurium were administered if more neuromuscular relaxation was required as warranted by the surgical procedure.

Heart rate and blood pressure were recorded before the initial dose of mivacurium and at 1-min intervals for the next 5 min after the initial dose. Tracheal intubation was performed after the additional 0.1 mg/kg dose of mivacurium in subgroups A1–A3 and B1–B3 and after the initial bolus dose of mivacurium in subgroups A4, A5, B4, and B5. In each subgroup tracheal intubation and surgical stimulation were delayed until 5 min after the initial mivacurium dose to allow uncomplicated assessment of the cardiovascular effects of mivacurium. Following tracheal intubation the cardiovascular parameters were recorded and thereafter every 5 min, and more frequently as indicated clinically.

Clinical conditions of intubation were rated according to the ease with which both laryngoscopy was performed and the endotracheal tube was passed as well as the patient's response. Conditions were considered excellent (score = 1) when the mouth could be opened easily and no movement of the vocal cords, diaphragm, or abdominal muscles was detected during or after intubation. When the jaw muscles were relaxed but some movement of the vocal cords or abdominal muscles was detected, conditions were rated as satisfactory (score = 2). When the vocal cords were moderately adducted and there was moderate coughing, the conditions were rated as poor (score = 3).

The train-of-four response was monitored throughout the surgical procedure. If the first response of the train-of-four (T1) was less than 75% of control, the residual neuromuscular blockade was antagonized with 0.03 mg/kg atropine and 0.3 mg/kg edrophonium. Clinical neuromuscular recovery was also assessed at the end of surgery and 1 h later in the recovery room. Signs of adequate reversal included effortless opening of the eyes, lifting of the head for 5 s, and in cooperative patients a grip strength commensurate with age.

The time to maximum twitch depression (onset time) was determined by measuring the time from the initial administration of mivacurium to the onset of maximum blockade. Twitch depression was expressed as per cent reduction of the first twitch in the train-of-four (T1) relative to control (pre injection). Recovery time was determined by measuring the time from the administration of the last dose of mivacurium to the return of the first twitch in the train-of-four (T1) to 5%, 25%, 50%, 75%, and 95% of control.

The dose–response curve for neuromuscular blockade was estimated by linear regression of the probit values corresponding to the percentage of neuromuscular blockade. The method of Litchfield and Wilcoxon was used for these estimations, as well as for testing the parallelism of the dose–response curves. Other appropriate comparisons were made by linear regression, Student's $t$ test, or $F$ test analysis of variance. Mean and standard error were calculated by standard formulae. Data were considered significant when $P < 0.05$.

In 27 patients clinical laboratory tests were performed before the administration of mivacurium and then again at 12–48 h postoperatively. These tests included urine analysis with specific gravity and sediment, CBC with WBC differential, Na, K, Cl, Ca, protein, Mg, SGOT, Alk Phos, CPK, SGPT, bilirubin, BUN, and creatinine.

**Results**

The mean age (±SEM) of the children studied was 5.6 ± 0.4 yr (range, 2–12 yr) and their mean weight was 22.9 ± 1.1 kg (range, 12–46 kg). There was no significant difference between the ages and the weights between the two groups and the subgroups.

**NEUROMUSCULAR EFFECTS**

The neuromuscular effects for subgroups A1–A3 and B1–B3 (those groups receiving small initial doses) are summarized in table 1. The ED$_{95}$ and ED$_{95}$ neuromuscular blocking doses in the halothane group were 0.051 and 0.095 mg/kg, respectively, and in the $N_2O$:O$_2$ narcotic
group 0.059 and 0.11 mg/kg, respectively. The two dose-response curves did not differ from parallelism (fig. 1). The subsequent mivacurium dose 0.1 mg/kg administered 5–6 min after the original dose caused 100% depression of the twitch in 86% of the patients and 92.6 ± 1.3% in the remainder.

In children receiving an ED₉₅ dose of mivacurium (subgroups A₄ and B₄) the maximum suppression of the twitch occurred in 3 ± 0.2 min, and recovery to 25% and 95% took 7.6 ± 0.8 and 15.2 ± 2.4 min, respectively (table 2). Administering 0.2 mg/kg produced 100% block in all patients; time to onset here was 1.8 ± 0.1 min, significantly less (P < 0.05) than the time to onset following the ED₉₅ dose. Recovery, however, was prolonged by only 3 min; the children recovered to 25% and 95% in 11.2 ± 0.8 and 18.4 ± 2.3 min, respectively.

In all phases of the study, mivacurium proved to be a short-acting neuromuscular blocking agent with recovery indices of 4.6 ± 0.6 min for 25–75% recovery and 9.7 ± 1.3 min for 5–95% recovery. Although in the dose-response phase of the study the children during halothane N₂O:O₂ anesthesia required less mivacurium than those anesthetized by N₂O:O₂ narcotic, the difference was not statistically significant. Also, the recovery rate was not affected by halothane. Children recovered from similar doses of mivacurium at similar rates whether they were anesthetized with or without halothane. (tables 1 and 2)

**Cardiovascular Effects**

In the absence of surgical stimulation and tracheal intubation, mivacurium did not cause any appreciable changes in the mean, systolic, or diastolic blood pressures at any of the doses studied, nor was there any significant change in mean heart rate. The concomitant changes in mean arterial pressure, heart rate, and the neuromuscular response in the first 5 min following 0.2 mg/kg mivacurium is depicted in figure 2. In the patients receiving large bolus doses of mivacurium (0.09–0.2 mg/kg), only two patients showed more than 20% diminution in blood pressure or the heart rate. These were in the halothane N₂O:O₂ groups. In the first one the heart rate declined

![Graph](image-url)

**Fig. 1.** The dose-response curves of mivacurium during N₂O:O₂ halothane (1% inspired) or N₂O:O₂ narcotic anesthesia.
Table 2. The Neuromuscular Effects of ED\textsubscript{95} and 2 X ED\textsubscript{95} Bolus Doses of Mivacurium in Children Anesthetized with Halothane N\textsubscript{2}O:O\textsubscript{2} (A\textsubscript{4} and A\textsubscript{3}) or N\textsubscript{2}O:O\textsubscript{2}: narcotic (B\textsubscript{4} and B\textsubscript{3})

<table>
<thead>
<tr>
<th>Group</th>
<th>Mivacurium Dose (mg/kg)</th>
<th>Max Block (%)</th>
<th>Injection to Maximum Block (min)</th>
<th>Intubation</th>
<th>Recovery to (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intubation</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>% Block at</td>
<td>5%</td>
</tr>
<tr>
<td>N\textsubscript{2}O:O\textsubscript{2}; halothane</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A\textsubscript{4}</td>
<td>0.09</td>
<td>86.5 ± 6.6</td>
<td>9.1 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>95.2 ± 2.5</td>
</tr>
<tr>
<td>A\textsubscript{3}</td>
<td>0.2</td>
<td>100</td>
<td>1.9 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td>100</td>
</tr>
<tr>
<td>N\textsubscript{2}O:O\textsubscript{2}; narcotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B\textsubscript{4}</td>
<td>0.11</td>
<td>99.4</td>
<td>3 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>89.5 ± 5.1</td>
</tr>
<tr>
<td>B\textsubscript{3}</td>
<td>0.2</td>
<td>100</td>
<td>1.5 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>99.2 ± 0.6</td>
</tr>
</tbody>
</table>

Data are mean ± SEM; n = 9 in all subgroups.

Gradually over 4 min from 95 beats/min to 74 beats/min and increased to 107 beats/min following tracheal intubation; there were no concomitant blood pressure changes in this patient. In the second patient following 0.2 mg/kg mivacurium the blood pressure decreased from 109/67 mmHg to 97/41 mmHg for 1 min and thereafter remained at 84/48 mmHg until tracheal intubation.

**Cutaneous Reaction**

Of the 90 patients studied, three manifested cutaneous reactions. The first was a 2-year-old child, anesthetized with halothane, who after the second mivacurium dose (0.1 mg/kg) developed maculopapular redness along the tract of the vein in which the drug was injected; in this patient the automatic blood pressure apparatus, which was on the same arm as the IV canula, started cycling just after the administration of mivacurium. The second patient was 12 yr old (also anesthetized with halothane) and developed a mild flush after the additional 0.1 mg/kg. The most prominent cutaneous reaction was in a 4-year-old child who was anesthetized with N\textsubscript{2}O:O\textsubscript{2} narcotic; after a dose of 0.2 mg/kg a maculopapular rash developed over the chest and neck. This rash lasted for 5 min and then resolved spontaneously. In this patient blood pressure decreased from 115/70 mmHg to 95/55 mmHg for about 1 min and then recovered spontaneously, whereas the heart rate increased from 115 to 119 beats/min.

**Tracheal Intubation**

In subgroups A\textsubscript{1}–A\textsubscript{3} and B\textsubscript{1}–B\textsubscript{3}, the patients in whom an initial small dose of mivacurium was followed approximately 5 min later by the standardized additional dose of 0.1 mg/kg, conditions for tracheal intubation rated excellent in 72% of the cases and satisfactory in 25%. In these patients the mean neuromuscular depression at the time of intubation was 96.9 ± 0.6%. Intubation attempted in the presence of at least 90% twitch suppression was successfully accomplished with relative ease. In two patients (3%) conditions were rated poor, 77% and 33% block were present during tracheal intubation of these patients.

In patients receiving 0.9 and 0.11 mg/kg doses, conditions were rated excellent in 62% and satisfactory in 38%, whereas in the 0.2 mg/kg groups conditions were excellent in 55% and satisfactory in 45%. In these patients tracheal intubation was not attempted until 5 or more min had elapsed after the administration of mivacurium.

**Reversal of Neuromuscular Effects**

In 17 patients reversal with atropine (0.03 mg/kg) and edrophonium (0.3 mg/kg) was attempted in the presence of a mean recovery to 43 ± 2% (11–75%); in these patients T\textsubscript{1} returned to 95% of control in 3.3 ± 0.6 min.

None of the patients (either those in whom reversal was attempted or those in whom recovery occurred spontaneously) showed any evidence of clinical neuromuscular

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**Fig. 2.** The changes in mean arterial pressure, heart rate, and neuromuscular response following the administration of 0.2 mg/kg mivacurium.
weakness at the completion of surgery or in the recovery room approximately 1 h later.

RELATION WITH PLASMA CHOLINESTERASE

The mean plasma cholinesterase of the patients studied was 9.25 ± 0.08 units and the dibucaine number was 87.8 ± 0.5%. In the patients anesthetized with N₂O:O₂ narcotic there was a significant correlation (P < 0.02) between plasma cholinesterase values and the recovery indices of 25–75% (r = 0.42) and 5–95% (r = 0.54). No such correlation was detected in the children anesthetized with halothane and nitrous oxide. Additionally, the recovery rates throughout could not be correlated with the dibucaine numbers. None of the patients studied had a markedly low cholinesterase level or dibucaine number.

LABORATORY TESTS

In the hemopoietic, renal, and hepatic laboratory tests performed preoperatively and postoperatively, there were no significant changes that could be attributed to the effect of mivacurium.

Discussion

Previous studies in adults have established that mivacurium is a safe and effective short-acting, nondepolarizing, neuromuscular blocking agent. The present study has demonstrated that mivacurium can be safely and efficaciously used in healthy children. Although comparisons of adult and pediatric response to the effects of mivacurium remain tentative, some observations can nonetheless be confidently offered. Studies in adults using single twitch stimuli during N₂O:O₂ narcotic anesthesia have found the ED₉₀ to be 0.059–0.052 mg/kg and the ED₉₅ to be 0.075–0.12 mg/kg. In the present study of children during N₂O:O₂ narcotic anesthesia, the ED₉₀ was 0.059 and ED₉₅ 0.11 mg/kg. The aforementioned studies used single-twitch stimulation, whereas we used train-of-four stimulation. The one adult study that did employ train-of-four stimulation found the ED₉₀ to be 0.041 and the ED₉₅ to be 0.058 mg/kg, values definitely lower than those of the children in our study. The only other study that has evaluated mivacurium in children used train-of-four stimuli but recorded the evoked electromyogram. The ED₉₀ was 0.057 mg/kg and the ED₉₅ was 0.124 mg/kg during halothane anesthesia. Values comparable to ours but higher than the adults. Consequently, we can speculate that children require more mivacurium (mg/kg) than adults to achieve comparable degrees of neuromuscular relaxation.

In comparing the recovery times from the effects of mivacurium in children in this study with those of adults in other studies, we find that children recover faster. The recovery indices (25–75% and 5–95%) in children are 4.6 ± 0.6 min and 9.7 ± 1.3 min, respectively, whereas in adults they are 6.8 ± 0.3 min and 14.1 ± 0.6 min, respectively. Furthermore, recovery from fixed doses is faster in children than in adults; following 0.08 mg/kg adults were shown to recover to 25% and 95% in 11.7 ± 0.5 and 20.2 ± 1.4 min, respectively; following a larger dose of 0.1 mg/kg they recovered to 25% and 95% in 14.2 ± 1.5 and 24.5 ± 1.6 min respectively. In our study of children receiving N₂O:O₂ narcotic anesthesia, recovery to 25% and 95% following a larger dose of 0.11 mg/kg occurred in 8 ± 0.5 and 16 ± 1.4 min. These times are less than those of adults despite the slightly smaller doses used in adults. Faster recovery times in children are also evident at the upper end of the dosage scale. After 0.2 mg/kg adults in two different studies recovered to 25% in 19.7 ± 1.8 min and 19.3 ± 2.0 min and to 95% in 30.6 ± 2.4 and 30.8 ± 3.2 min, whereas in children recovery to 25% after 0.2 mg/kg occurred in 11.4 ± 0.8 min and to 95% in 18.7 ± 2 min.

In comparing the effective doses of mivacurium in children anesthetized with the two methods dictated by our study protocol, we observed that during halothane nitrous oxide anesthesia the effective doses are slightly less than those during balanced anesthetisa (fig. 1). This difference was not statistically significant. This difference has recently been seen with continuous infusion, where during balanced anesthesia children required a higher mivacurium infusion rate than that required during halothane anesthesia to maintain comparable degrees of neuromuscular relaxation. Again, when we compare the effects of large identical doses of mivacurium in the two major groups described herein we find that recovery rates are practically the same. These data indicate that over a short duration the effects of a moderate concentration (1%) of halothane are negligible.

A comparison of the potency of mivacurium with the newer intermediate-acting, neuromuscular blocking agents shows mivacurium to be between atracurium and vecuronium. In children during halothane anesthesia with train-of-four stimulation, the ED₉₀ and ED₉₅ of atracurium are 0.11 mg/kg and 0.17 mg/kg, respectively while the ED₉₀ and ED₉₅ of vecuronium are 0.033 mg/kg and 0.06 mg/kg. The comparative values of mivacurium are 0.059 and 0.11 mg/kg, respectively. The duration of action of mivacurium, however, is shorter as expected. The 5–95% recovery of mivacurium is 9.7 ± 1.3 min as opposed to 23 ± 2.3 min with vecuronium and 28.4 ± 1.5

min with atracurium. Similarly, the recovery indices (25–75%) are shorter being 4.6 ± 0.6 min as opposed to 9.4 ± 0.8 min with vecuronium and 12.3 ± 0.9 min with atracurium. The duration of action of mivacurium is therefore about one-third that of atracurium and about one-half that of vecuronium. This shorter duration with mivacurium is not accompanied by a faster onset of action. Following twice the ED95 the maximum depression of the twitch response occurs in 1.6–1.9 min with mivacurium, a value comparable to that of 2 min reported with atracurium and vecuronium in children.11,12 In this respect mivacurium does not compare with the rapid onset of succinylcholine of about 45 s in children.13 Another significant difference between mivacurium and intermediate-acting neuromuscular blockers is that increasing the dosage does not markedly increase the duration of action. In our children increasing the dose of mivacurium from 1 × ED95 to approximately twice the ED95 prolonged the duration of action by only 3 min (20%) while shortening the onset to maximum depression from 3 to 1.7 min. This is in contrast to vecuronium in which increasing the dose from 0.055 mg/kg to 0.1 mg/kg has increased the duration of action (maximum depression to 90% recovery) from 20 to 36 min.14

In vitro evidence of hydrolysis by plasma cholinesterase has been noted with mivacurium.1 In the present study children during N2O:O2 narcotic anesthesia were found to demonstrate a significant correlation between plasma cholinesterase and the standard recovery indices of mivacurium; children with the higher cholinesterase values had the shorter duration of action. This factor reinforces the observation that plasma cholinesterase is involved in the degradation metabolism of mivacurum in vivo. The fact that this correlation was present in only one group of our patients, coupled with the fact that it has been observed in some studies but not in others, might possibly indicate the presence of other routes of metabolism or excretion.2

In conclusion, we found that mivacurium is a short-acting neuromuscular blocking agent that can be safely used in children. It has a duration of action approximately one-third that of atracurium and one-half that of vecuronium.

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