Mivacurium Neuromuscular Block at the Adductor Muscles of the Larynx and Adductor Pollicis in Humans

Benoit Piaud, M.D.,* Bertrand Debaene, M.D.,† Frank Lequeau, M.D.,* Claude Meistelman, M.D.,‡ Francois Donati, M.D., Ph.D.§

Background: Laryngeal muscles must be paralyzed for tracheal intubation. Time to peak effect (onset time) is shorter and intensity of blockade is less at laryngeal muscles compared with the adductor pollicis. The authors' aim in this study was to determine the neuromuscular effects of mivacurium at the laryngeal adductor muscles and the adductor pollicis.

Methods: In 22 adults, anesthesia was induced and maintained with propofol and alfentanil. The force of contraction of the adductor pollicis was recorded, and the laryngeal response was evaluated by measuring the pressure change in the cuff of a tracheal tube positioned between the vocal cords after train-of-four stimulation. Mivacurium (0.07 mg·kg⁻¹ or 0.14 mg·kg⁻¹) was given intravenously (10 s).

Results: With 0.07 mg·kg⁻¹ mivacurium, onset time was 151 ± 40 s (mean ± SD) at the larynx and 241 ± 79 s at the adductor pollicis, respectively (P < 0.005). Maximum block was 78 ± 18% and 95 ± 8%, respectively (P < 0.002), and time to 90% recovery was 11.1 ± 2.9 min and 23.3 ± 7.6 min, respectively (P < 0.001). With 0.14 mg·kg⁻¹ mivacurium, onset time also was more rapid at the vocal cords (137 ± 20 s) than at the adductor pollicis (201 ± 59 s, P < 0.01). Maximum block was 90 ± 7% and 99 ± 1% (P < 0.005), and time to 90% recovery was 16.4 ± 4.9 min and 27.4 ± 7.8 min, respectively (P < 0.01).

Conclusions: With mivacurium, onset and recovery are faster at the laryngeal muscles, but block is less intense than at the adductor pollicis. A dose greater than 0.14 mg·kg⁻¹ mivacurium is necessary to ensure complete relaxation at the vocal cords. (Key words: Larynx; vocal cords. Monitoring: neuromuscular blockade. Neuromuscular relaxants: mivacurium. Skeletal muscles: adductor pollicis; laryngeal adductor muscles.)

NEUROMUSCULAR blockade occurs more rapidly at the adductor muscles of the larynx than at the adductor pollicis after injection of vecuronium,¹ rocuronium,² or succinylcholine.³ Differences were observed between the intubating conditions and the intensity of neuromuscular block at the adductor pollicis.⁴ It is likely that intubating conditions are related more closely to the degree of neuromuscular block at the laryngeal adductor muscles. The dose of vecuronium¹ and rocuronium² required for laryngeal muscle block is larger than for comparable adductor pollicis block. The laryngeal muscles can be considered resistant to the effects of nondepolarizing muscle relaxants, and the duration of action of neuromuscular block is shorter at the vocal cords than at the adductor pollicis after injection of vecuronium¹ and rocuronium.²

The clinical pharmacology to date indicates that mivacurium has an onset of action at the adductor pollicis comparable with that of equipotent doses of atracurium and vecuronium, but its duration of action is one third to one half as long as that of those compounds.⁵ These onset and duration data were obtained at the adductor pollicis muscle. Laryngeal adductor muscles, which close the glottis, are important clinically, and the time course of mivacurium blockade on these muscles has not been measured.

Therefore, our aim in this study was to determine the onset time, intensity, and duration of action of mivacurium-induced neuromuscular block on the laryngeal adductors and the adductor pollicis muscles in humans.
Materials and Methods

The protocol was approved by the Ethical Committee of the University Paris Sud. Twenty-two American Society of Anesthesiologists physical status 1 or 2 patients, aged 30–62 yr, undergoing elective surgical procedures were studied after giving written informed consent. Exclusion criteria included abnormal upper airway, previous head and neck surgery or radiotherapy, and deviation from ideal body weight by more than 20%. No patient had any disease or was taking drugs known or suspected to interfere with neuromuscular transmission. Patients with cardiovascular, respiratory, hepatic, or renal disease also were excluded from the study.

No premedication was used. On arrival in the operating room, blood pressure was measured noninvasively with a cuff attached to the arm not involved with neuromuscular monitoring. Pulse oxymetry and electrocardiography were monitored continuously.

Anesthesia was induced with 2–2.5 mg·kg⁻¹ propofol and 10–20 µg·kg⁻¹ alfentanil intravenously. Intubation was performed without neuromuscular relaxant, and no local anesthetic drug was given intratracheally. The system to monitor contraction of laryngeal adductor muscles is described elsewhere. To monitor the contraction of the laryngeal adductor muscles, a Mallinckrodt tracheal tube (ID 7.5 mm; Athlone, Ireland) was used. The inflatable cuff of the tracheal tube was positioned between the vocal cords under direct vision and inflated with air to a pressure of at least 10–12 mmHg sufficient to prevent leaks. The cuff was connected to an air-filled Hewlett-Packard pressure transducer. Ventilation was controlled mechanically to maintain the partial pressure of carbon dioxide, as measured by capnography, between 30 and 40 mmHg. Anesthesia was maintained with 10–15 mg·kg⁻¹·h⁻¹ propofol and intermittent boluses of 5–10 µg·kg⁻¹·h⁻¹ alfentanil. No halogenated anesthetics or nitrous oxide were used throughout the study.

Bilateral adduction of the vocal cords was produced by supramaximal square wave stimuli (0.2 ms in duration, 60–70 mA) of the recurrent laryngeal nerve. A negative cutaneous electrode was placed on the notch of the thyroid cartilage, and the positive electrode was placed on either the sternum or the forehead. Supramaximal train-of-four stimulations were applied every 10 s with a Curaremeter Module 1 nerve stimulator (Bio-Industry, Boulogne, France). The response of the laryngeal adductor muscles was evaluated by measuring the pressure change produced in the cuff of the tracheal tube with adduction of the vocal cords.

The ulnar nerve was stimulated at the wrist with surface electrodes, using 2-Hz train-of-four stimulation every 10 s with a 0.2 ms supramaximal square wave stimuli (40–60 mA). The force of contraction of the adductor pollicis was measured with a Curaremeter Module 2 (Bio-Industry). Responses from the laryngeal adductor muscles and adductor pollicis were displayed on an oscilloscope and recorded simultaneously on paper. After a stable baseline was obtained (5–5 min), a dose close to the dose that depressed twitch tension by 95% (ED₉₅) and twice the ED₉₅ for mivacurium at the adductor pollicis, 0.07 (n = 11) or 0.14 (n = 11) mg·kg⁻¹, respectively, was injected by random allocation as an intravenous bolus for 10 s. After maximum block was attained, the interval between train-of-four stimulations was increased to 20 s. Recording was continued until recovery of the first twitch response (T₁) of the train-of-four to 90% of control value at both muscles.

The following parameters were measured: time to peak effect or onset time (time from the end of the injection until maximum T₁ block), maximum block, and times from the injection to 25%, 75%, and 90% T₁ spontaneous recovery. The recovery index (time from 25% to 75% T₁ spontaneous recovery) was then calculated. The results are expressed as mean ± SD. The results obtained at the larynx and the adductor pollicis were compared using a paired signed-rank test. A P value of 0.05 or less was considered to indicate statistically significant differences.

Results

The patients’ demographic data are presented in table 1. The two groups did not differ significantly with respect to age, height, or weight. Maximum neuromuscular block occurred 60–90 s sooner at the vocal cords than at the adductor pollicis with either dose (table 2). With 0.07 mg·kg⁻¹, onset time was 241 ± 79 s and 151 ± 40 s at the adductor pollicis muscles, respectively (P < 0.01). Maximum block was significantly greater at the vocal cords than at the adductor pollicis (table 2). With 0.14 mg·kg⁻¹, adductor pollicis was achieved 1 s sooner at the vocal cords than at the adductor pollicis. The recovery index did not differ significantly between two muscles.

Discussion

With this study, it is demonstrated that a single bolus of mivacurium produces a higher and quicker block at the vocal cords than at the adductor pollicis, with maximum block occurring sooner. The study is limited by the small sample size and with small patient numbers in each group. Recovery of muscle function was calculated using the recovery index. However, there are no standardized methods for measuring recovery of muscle function. In this study, the anesthetized patients were maintained with inhalation anesthesia, without the use of any additional agents to reduce the recovery time.
MIVACURIUM AND LARYNGEAL MUSCLES

Table 2. Onset Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dose (mg·kg⁻¹)</th>
<th>Larynx</th>
<th>Adductor Pollicis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum block (%)</td>
<td>0.07</td>
<td>78 ± 18</td>
<td>95 ± 8</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>0.14</td>
<td>90 ± 7</td>
<td>99 ± 1</td>
<td>0.002</td>
</tr>
<tr>
<td>Onset (s)</td>
<td>0.07</td>
<td>151 ± 40</td>
<td>241 ± 79</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>0.14</td>
<td>137 ± 20</td>
<td>201 ± 59</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* Paired t test comparing the values between the two muscles for each dose.

and 151 ± 40 s at the adductor pollicis and the laryngeal adductor muscles, respectively (P < 0.005). After 0.14 mg·kg⁻¹, onset time was 201 ± 59 s and 137 ± 20 s, respectively (P < 0.01).

Maximum block was significantly greater at the adductor pollicis than at the vocal cords for both doses (table 2). With 0.14 mg·kg⁻¹, complete block at the adductor pollicis was achieved in all patients except 1, whereas complete block at the laryngeal adductor muscles was achieved in only 1 of 11 patients.

With both doses, recovery occurred 10–12 min sooner at the vocal cords than at the adductor pollicis (table 3) in all subjects. Typically when recovery was 90% complete at the vocal cords, it was only 25% at the adductor pollicis. However, with both doses, recovery index did not differ significantly between the two muscles.

Discussion

With this study, it is demonstrated that the responses to a single bolus of mivacurium are different between the laryngeal adductor muscles and the adductor pollicis. Maximum block at the laryngeal adductors is less than at the adductor pollicis, but onset time is faster at the larynx. Recovery of laryngeal muscles occurs much sooner than at the adductor pollicis. These results are quantitatively similar to those obtained with vecuronium and rocuronium under similar conditions. However, there are quantitative differences among nondepolarizing muscle relaxants concerning onset time, duration of action, and recovery index.

In this study, the anesthetic protocol (propofol, fentanyl, or alfentanil, without nitrous oxide or halogenated agent) was similar to that of previous studies on the neuromuscular blocking effects of several muscle relaxants on the laryngeal adductor muscles. The onset to maximum block for mivacurium at the laryngeal adductor muscles and adductor pollicis was longer than for rocuronium. After injection of 0.140 mg·kg⁻¹ mivacurium, the mean onset time at the vocal cords was 2.3 min compared with 1.4 min after injection of 0.5 mg·kg⁻¹ rocuronium. These results are consistent with previous clinical studies in which it was demonstrated that conditions usually were appropriate for intubation 2 min after mivacurium administration. 9,10

After administration of 0.14 mg·kg⁻¹ mivacurium, mean maximum block at the vocal cords was 90%, and full paralysis occurred in only 1 of 11 patients. For both doses given, maximum block was less at the larynx than at the adductor pollicis. Comparison of the effects of both doses at the laryngeal adductor muscles suggests that more than twice the ED₉₅ at the adductor pollicis is necessary to paralyze the vocal cords. This suggests a high dose-response ratio for mivacurium between the laryngeal adductor muscles and the adductor pollicis. The sparing effect at the vocal cords has been demonstrated after vecuronium and rocuronium. 2

The reason for the resistance of the laryngeal adductor muscles to the effects of nondepolarizing blockers is unknown. Muscle fiber type and size could influence the sensitivity to muscle relaxants. 11–13 Ibebuo and Hall 11 suggested that sensitivity increases with size. This hypothesis appears to be supported by the fact that, in humans, laryngeal muscles contain very small fibers, whereas larger fibers are found in peripheral muscles. Therefore, it might be expected that, after the recommended intubating dose (i.e., 0.15 mg·kg⁻¹) of mivacurium, the laryngeal adductor muscle block might not be sufficient to perform tracheal intubation under excellent conditions. The original design of this

Table 3. Recovery Characteristics

<table>
<thead>
<tr>
<th>Recovery (%)</th>
<th>Dose (mg·kg⁻¹)</th>
<th>Larynx (min)</th>
<th>Adductor Pollicis (min)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>25⁺</td>
<td>0.07</td>
<td>4.8 ± 1.7</td>
<td>13.2 ± 6.6</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>0.140</td>
<td>5.7 ± 2.1</td>
<td>16.2 ± 4.6</td>
<td>0.002</td>
</tr>
<tr>
<td>75</td>
<td>0.07</td>
<td>8.7 ± 2.7</td>
<td>19.9 ± 6.8</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>0.140</td>
<td>12.8 ± 3.9</td>
<td>23.4 ± 6.2</td>
<td>0.002</td>
</tr>
<tr>
<td>90</td>
<td>0.07</td>
<td>11.1 ± 2.9</td>
<td>23.3 ± 7.6</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>0.140</td>
<td>16.4 ± 4.9</td>
<td>27.4 ± 7.8</td>
<td>0.002</td>
</tr>
<tr>
<td>TH25–75</td>
<td>0.07</td>
<td>5.1 ± 1.4</td>
<td>6.8 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.140</td>
<td>7.2 ± 2.7</td>
<td>7.2 ± 1.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
TH25–75 = recovery index; NS = not significant.
* Two patients did not reach 75% block at the larynx; thus, 25% recovery was expressed for nine patients as the recovery index did.
study did not allow determination of the intubating conditions after 0.14 mg·kg⁻¹ mivacurium because it was administered after intubation. However, in two studies, it was suggested that good or excellent intubating conditions in all patients are achieved only with a dose greater than 0.15 mg·kg⁻¹. The major drawbacks of these studies were the absence of a control group without muscle relaxants and the small number of patients included.

Another factor that may contribute to inadequate intubating conditions in some patients is the rapid elimination of mivacurium in plasma. Researchers have not examined intubating conditions at different intervals after mivacurium or after induction regimens that do not ensure adequate intubating conditions without paralysis. However, on the basis of our study, paralysis peaks at the laryngeal muscles 2–3 min after mivacurium administration, then recovers rapidly. This brief window of peak paralysis suggests that intubating conditions will be optimal for only a brief period. Because of mivacurium’s rapid hydrolysis by plasma cholinesterase, blood concentrations decrease rapidly when compared with currently available nondepolarizing muscle relaxants. Time to peak effect is attained earlier at the laryngeal muscles than at the adductor pollicis. This suggests that concentrations begin to decrease at the laryngeal muscles before reaching their peak at the adductor pollicis. These findings suggest a more rapid equilibration (larger kₑ) between plasma concentration and those at the airway compared with the adductor pollicis.

Plaud et al. reported that for rocuronium, kₑ at the laryngeal muscles was greater than at the adductor pollicis. This might explain why in two patients who received 0.14 mg·kg⁻¹ mivacurium, 25% recovery at the laryngeal adductor muscles was observed before maximum blockade at the adductor pollicis (fig. 1).

The duration of action at the laryngeal adductor and adductor pollicis muscles is shorter after mivacurium than after rocuronium when equipotent doses are given (0.14 mg·kg⁻¹ mivacurium: 0.5 mg·kg⁻¹ rocuronium). T₁ at the laryngeal adductor muscles reached 90% of control in 16.4 min after mivacurium versus 22 min after rocuronium. T₁ recovery to 90% at the adductor pollicis was obtained in 27.4 min after mivacurium versus 37 min after rocuronium. Therefore, mivacurium has a shorter duration of action at the laryngeal adductor muscles and at the adductor pollicis than does rocuronium. At approximately equipotent doses (slightly less than 2 × ED₉₅), duration of action of succinylcholine is shorter than that of mivacurium. With mivacurium, 25% twitch height recovery at the laryngeal adductor muscles occurred in 5.7 min after 0.14 mg·kg⁻¹ and 2.1 min after 0.5 mg·kg⁻¹ succinylcholine. However, early reversal of mivacurium-induced neuromuscular block could shorten the duration of laryngeal and respiratory muscle block and allow a rapid return to spontaneous ventilation.

In conclusion, after administration of 0.07 and 0.14 mg·kg⁻¹ mivacurium, the laryngeal adductor muscles are more resistant than the adductor pollicis. Onset time and duration of neuromuscular blockade are shorter at the vocal cords than at the adductor pollicis. Further studies are required to determine the dose of mivacurium that could achieve complete paralysis of the laryngeal adductor muscles in all patients.

References

MIVACURIUM AND LARYNGEAL MUSCLES


