Pharmacodynamics and the Plasma Concentration of Mivacurium during Spontaneous Recovery and Neostigmine-facilitated Recovery

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Background: The authors examined the plasma concentrations of the isomers of mivacurium and its pharmacodynamics during spontaneous and neostigmine-facilitated recovery after a mivacurium infusion.

Methods: Sixteen patients receiving nitrous oxide-opioid anesthesia received 0.25 mg/kg mivacurium. Patient response to a mivacurium infusion was begun and adjusted to maintain 95-99% neuromuscular block. The infusion was discontinued after 90 min and muscle strength allowed to recover either spontaneously or after neostigmine/glycopyrrolate (0.05/0.01 mg/kg). Plasma concentrations of the isomers of mivacurium after discontinuation of the infusion were determined using an HPLC assay. Differences between the groups were determined using a one-way analysis of variance with a Bonferroni-corrected t test or Student t test as appropriate. P ≤ 0.05 was considered significant.

Results: Differences in the times for recovery to a train-of-four ratio of 70% did not achieve statistical significance (mean ± SD, 13.3 ± 6.0 vs. 16.3 ± 2.5 min for the neostigmine and spontaneous groups, respectively). Plasma cholinesterase activity decreased significantly from baseline values after administration of neostigmine (5.88 ± 0.21 vs. 0.43 ± 0.04 U/ml plasma). Plasma concentrations of the trans-trans isomer were significantly greater in the neostigmine group than in the spontaneous recovery group 5, 6, 8, and 10 min after discontinuation of the infusion. Differences in the plasma concentration of the cis-trans isomer did not achieve statistical significance.

Conclusions: Although administration of neostigmine decreased plasma cholinesterase activity and caused the trans-trans isomer to remain in the plasma at higher concentration, it did not delay recovery from mivacurium-induced block. (Key words: Antagonism; mivacurium; neostigmine; plasma cholinesterase; stereoisomers.)

MIVACURIUM'S potent cis-trans and trans-trans isomers are metabolized by plasma cholinesterase.1-3 Mivacurium's duration of action is prolonged in patients with hepatic failure, renal failure, and advanced age.4,5 This alteration in the pharmacodynamic behavior of the relaxant is secondary to decreased plasma cholinesterase activity in these patient populations.5-10 Anticholinesterase agents have typically been used to hasten the process of recovery from nondepolarizing neuromuscular block. Because of the short duration of action, however, the argument has been made that pharmacologic antagonism of residual mivacurium-induced neuromuscular block need not be routine. Furthermore, neostigmine decreases plasma cholinesterase activity and may inhibit the breakdown of mivacurium, possibly resulting in delayed plasma clearance and a prolonged effect.11,12 Consistent with this, it has been reported to either prolong recovery from profound mivacurium-induced neuromuscular block in vivo15 or to poorly antagonize block during a mivacurium infusion.12 Other studies, however, have found neostigmine to be an effective antagonist of residual mivacurium-induced neuromuscular block.14,16 This study was undertaken to reconcile the results of these studies regarding the influence of neostigmine on the elimination of mivacurium and the dynamics of recovery from mivacurium-induced neuromuscular block. To this end we simultaneously examined the plasma concentrations of the cis-trans and trans-trans isomers of mivacurium as well as the relaxant's pharmacodynamic behavior during spontaneous recovery.
plasma cholinesterase activity was determined before and during recovery from mivacurium-induced neuromuscular block.

**Methods**

After approval of the protocol by the Human Rights in Research Committee at The New York Hospital-Cornell Medical Center, 16 male patients with American Society of Anesthesiologists physical status I or II (ranging in age from 19–51 yr), scheduled to undergo lengthy elective surgical procedures not requiring neuromuscular block, consented to participate in the study. Upon enrolling to participate in the study, patients were randomly assigned to be in one of two study groups: spontaneous recovery or neostigmine-facilitated recovery (n = 8 per group).

Patients enrolled in the study were free of hepatic, renal, cardiopulmonary, and neuromuscular disease. None had a history suggestive of reduced plasma cholinesterase activity. Patients were not enrolled in the study if they had been exposed to steroids within the 30 days before the study or antibiotics (with the exception of penicillins, cephalosporins, or tetracycline), diuretics, penicillamine, or procainamide within the 7 days before the study; phenytoin, carbamazepine, theophylline, tricyclic antidepressants, calcium-channel blockers, lithium, or procainamide within the 7 days before the study or antibiotics (with the exception of penicillins, cephalosporins, or tetracycline), diuretics, quinidine, or lidocaine within the 48 h before the study.

Upon arrival at the operating room, routine monitors (electrocardiogram, automatic blood pressure cuff, and pulse oximeter) were placed. In addition, an intravenous catheter appropriate for the surgery was placed. While breathing 100% oxygen through an anesthesia face mask, patients received midazolam (2–6 mg) and fentanyl (2–4 µg/kg) intravenously. A 16-gauge intravenous catheter was inserted in the arm not receiving intravenous fluids, and venous blood was obtained for baseline sampling (plasma cholinesterase activity using butyrylthiocholine as the substrate, dibucaine number, and mivacurium isomer concentration).

One percent lidocaine was injected subcutaneously over the course of the distal ulnar nerve, and 23-gauge steel needle electrodes were inserted for neuromuscular stimulation. The ulnar nerve was then stimulated with supramaximal train-of-four stimulation every 12 s for at least 3 min. The stimulus was delivered from a Grass (Quincy, MA) S88 stimulator in conjunction with a Grass model FT-10 applied to the thumb and recorded on a Grass model 7 polygraph. The patients’ responses to mivacurium were quantitated by the heights of their responses to neuromuscular stimulation.

General anesthesia was induced with thiopental (3–5 mg/kg). After the loss of consciousness, patients received a total of 0.25 mg/kg mivacurium administered as two separate boluses separated by 30 s (0.15 mg/kg followed by 0.10 mg/kg). Supplemental thiopental was administered if it was deemed necessary to maintain adequate anesthesia. The patients’ tracheae were intubated 60 s after administration of the second dose of relaxant. Mechanical ventilation was instituted. Esophageal temperature was measured continuously and maintained between 35.5°C and 37°C with a Bair Hugger (Augustine Medical, Eden Prairie, MN) and warmed intravenous fluids.

Anesthesia was maintained with oxygen and nitrous oxide (50%/70%) and supplemental doses of fentanyl and thiopental as indicated clinically. Once the first twitch (T₁) in the train-of-four response had recovered to 25% of its baseline height, a mivacurium infusion was begun at 10 µg·kg⁻¹·min⁻¹ and adjusted to maintain 95–99% block of T₁. The infusion was discontinued after 90 min, and T₁ allowed to recover spontaneously (control group). One minute after discontinuation of the mivacurium infusion, patients assigned to the neostigmine treatment group received neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg).

Venous blood samples (5 ml each) were obtained at 30, 45, 60, 70, and 89 min after the start of the mivacurium infusion to determine the baseline plasma concentrations of each of the mivacurium isomers, and at 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 15, 20, 30, 45, 60, 90, 120, and 240 min after discontinuation of the mivacurium infusion. Immediately after collection, the blood was transferred into a Vacutainer (Becton Dickinson, Franklin Lakes, NJ) containing ethylene diaminetetraacetic acid as an anticoagulant and 400 µl of the plasma cholinesterase inhibitor phospholene iodide (0.25%), mixed thoroughly, and placed on ice. This process was completed within 15 s from the beginning of sample collection. The blood samples were then centrifuged, and the plasma was decanted and frozen at −70°C. Later, the plasma samples were thawed and analyzed using a stereospecific high-performance liquid chromatographic method with fluorometric detection of the isomers of mivacurium. The coefficient of variation of the assay was 4.2% for the...
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trans-trans isomer and 4.1% for the cis-trans isomer. The lower limit of quantitation was 5 ng/ml. The extraction efficiencies for the trans-trans and cis-trans isomers were 60.0% and 56.6%, respectively.

At 2, 6, 20, 45, and 90 min after discontinuation of the infusion, 5-ml venous blood samples were obtained for determination of plasma cholinesterase activity. The mean plasma concentrations of the cis-trans and trans-trans isomers were determined in each patient during a 90-min infusion to maintain 95-99% neuromuscular block by averaging three to five plasma concentration values obtained 30-90 min after beginning the infusion. The results of any sample taken within 10 min of changing the mivacurium infusion rate were disregarded in the calculation of individual patient baseline plasma concentrations of the isomers of mivacurium. In all but three patients, all changes made in the mivacurium infusion rate were made in the first 20 min of the infusion. In the three patients in whom more changes were made (one in the spontaneous group and two in the neostigmine group), infusion rates varied only as much as 3 to 5 μg · kg⁻¹ · min⁻¹. In one patient this meant that the infusion rate ranged from 7 to 9 μg · kg⁻¹ · min⁻¹, and in the third from 6 to 8 μg · kg⁻¹ · min⁻¹. The baseline isomer concentrations for patients in each study group were averaged together to determine a mean baseline concentration. Plasma concentrations after discontinuation of the infusions were compared with this mean value.

The plasma concentrations of the cis-cis isomer after administration of neostigmine were not studied because it makes up approximately only 5% of the mivacurium administered, because it is relatively impotent in terms of its neuromuscular blocking activity, and because its clearance is not related to plasma cholinesterase activity.²

The response to neuromuscular stimulation was monitored for the depth of relaxation during the mivacurium infusion. The times to recovery of 25%, 75%, and 95% T₁ as well as train-of-four ratios of 70% and 90% were measured.

Results are presented as mean ± SD. Differences between the study groups regarding demographics, plasma cholinesterase activity, and pharmacodynamics were determined using the Student t test. Differences between the groups in isomer concentrations at different times were determined using a one-way analysis of variance with a Bonferroni-corrected t test. P < 0.05 was considered statistically significant.

Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>Study Group</th>
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<tbody>
<tr>
<td></td>
<td>Spontaneous</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>34.5 ± 8.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.7 ± 7.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178.5 ± 6.0</td>
</tr>
<tr>
<td>Plasma cholinesterase activity (units/l)</td>
<td>6.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>(4.5-9.3)</td>
</tr>
<tr>
<td>Dibucaine number</td>
<td>85.5 ± 4.0</td>
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<tr>
<td></td>
<td>(78.0-92.7)</td>
</tr>
</tbody>
</table>

Values are mean ± SD (range).

**Results**

The study groups were comparable in terms of age, weight, and height, as shown in table 1. At discontinuation of the infusion of mivacurium, they were also similar in terms of end-tidal carbon dioxide pressure (spontaneous, 29.1 ± 2.8 mmHg; neostigmine, 29.1 ± 2.9 mmHg) and esophageal temperature (spontaneous, 35.5 ± 0.5°C; neostigmine, 35.4 ± 0.7°C). Periods of baseline stimulation were also similar (spontaneous 8.7 ± 4.8 min; neostigmine 6.9 ± 2.7 min). Mean dibucaine number and baseline plasma cholinesterase activity were the same in the study groups, as demonstrated in table 1. The normal range for dibucaine numbers (percentage inhibition) using our methodology is 81-86.¹⁹ The mivacurium used in this study consisted of 34% cis-trans isomer, 62% trans-trans isomer, and 4% cis-cis isomer.

The mivacurium infusion rate required to maintain a stable depth of neuromuscular block did not differ significantly between the two study groups (spontaneous, 8.6 ± 1.9 μg · kg⁻¹ · min⁻¹; range 5.0-11.0 μg · kg⁻¹ · min⁻¹; neostigmine, 7.9 ± 2.3 μg · kg⁻¹ · min⁻¹; range 3.8-10.1 μg · kg⁻¹ · min⁻¹). The depth of neuromuscular block at discontinuation of the mivacurium infusion also did not differ significantly between the study groups (spontaneous, 97.6 ± 0.8%; range, 95.9-98.2%; neostigmine, 96.2 ± 2.9%; range, 90.5-99.8%).

As demonstrated in table 2, during the early phase of recovery (end of infusion to 25%, 75%, or 95% T₁), recovery occurred more quickly in the neostigmine group than in the spontaneous-recovery study group.

Individual patient plasma concentration-time data are shown in figure 1. Mean plasma concentrations of the trans-trans and cis-trans isomers are shown in table 3. As is shown in figure 2, plasma concentrations of the trans-trans isomer, expressed as percentage of baseline

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Table 2. Pharmacodynamics of Recovery

<table>
<thead>
<tr>
<th>Time (min) from End of Infusion to:</th>
<th>Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spontaneous</td>
</tr>
<tr>
<td>25% T1</td>
<td>6.9 ± 1.6</td>
</tr>
<tr>
<td>75% T1</td>
<td>11.5 ± 1.8</td>
</tr>
<tr>
<td>95% T1</td>
<td>14.7 ± 2.8</td>
</tr>
<tr>
<td>70% T4:T1 ratio</td>
<td>16.3 ± 2.5</td>
</tr>
<tr>
<td>90% T4:T1 ratio</td>
<td>17.7 ± 1.3</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*P < 0.001.
† P < 0.05.

(mean concentration during infusion), were significantly greater in the neostigmine group than in the spontaneous recovery group at 5, 6, 8, and 10 min after discontinuation of the mivacurium infusion. There were no significant differences in the plasma concentrations of the cis-trans isomer in the two study groups (fig. 2).

As demonstrated in figure 3, there was a significant decrease in plasma cholinesterase activity from baseline values in the neostigmine study group after administration of the anticholinesterase. The peak plasma decrease in cholinesterase activity occurred at 2 min. Plasma cholinesterase activity in the neostigmine group did not recover to only 45% of baseline values at 90 min after discontinuation of the mivacurium infusion and 89 min after administration of the anticholinesterase.

Discussion

Plasma concentrations of the trans-trans isomer of mivacurium were significantly higher in the study group receiving neostigmine than in the group allowed to recover spontaneously from mivacurium-induced neuromuscular block at 5, 6, 8, and 10 min after discontinuation of the infusion. The increased plasma concentration of the trans-trans isomer did not, however, delay recovery of neuromuscular function.

The pharmacodynamics of spontaneous recovery from mivacurium-induced block reported in this study (end of infusion to 95% recovery of T1 of 14 min, and end of infusion to 75% recovery of T1 of 11 min) are similar to what has been previously reported. The extent to which recovery was shortened by the administration of anticholinesterases (3-5 min), although similar, is not as profound in this study as has been previously reported (5-8 min). Our finding that the complete recovery of neuromuscular function after antagonism of relatively profound mivacurium-induced neuromuscular block with neostigmine is not significantly shortened is not surprising. A partial explanation for the less efficacious pharmacologic antagonism of mivacurium-induced neuromuscular block by neostigmine observed in this study is the depth of neuromuscular block at which the anticholinesterase was administered. Neuromuscular block in all patients at the time of discontinuation of the infusion and administration of anticholinesterase ranged from 90.5% to 99.8% suppression of T1. As described by Beemer et al., the time to recovery of neuromuscular function is a function of two processes—the depth of neuromuscular blockade at the time of anticholinesterase administration and the rate of spontaneous recovery from neuromuscular blockade. At profound levels of neuromuscular block, for example, > 90% block of T1, Beemer et al. found that the rate of spontaneous recovery was the factor that had the greater effect on the time required for recovery to a train-of-four ratio of 70%. Studies of edrophonium and neostigmine have identified a limit to the depth of neuromuscular block that can be effectively antagonized by anticholinesterase administration in that recovery times are not reduced by the addition of anticholinesterases if antagonism is attempted during profound levels of blockade.

Whether the slight decrease of 3 min in recovery times that we observed after the administration of neostigmine warrants its routine use for antagonism of profound mivacurium-induced neuromuscular block remains to be determined. There certainly does not seem to be a pharmacodynamic reason to avoid neostigmine after mivacurium. Kao and Le found that neostigmine administration significantly prolonged recovery to T1 of 95% and train-of-four ratios of 70% or 90%. This may have occurred because they attempted antagonism at 97-99% block as determined by the electromyogram, a profound depth of block at which no mechanical activity may ordinarily be detected. We administered anticholinesterase at deep levels of neuromuscular block, and recovery to T1 of 95% and train-of-four ratios of 70% or 90% certainly was not prolonged. Other possible explanations for the difference in study results are that Kao and Le’s study was performed during use of an isoflurane anesthetic, and a larger dose of neostigmine was used. The use of larger doses of anticholinesterase may have resulted in greater enzyme inhibition. Patients in their spontaneous recovery group recovered neuromuscular function over a time course similar to data that have been previously published. In other studies, the presence of volatile agents has been shown to slow spontaneous recovery from nondepolarizing

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neuromuscular block. In our study, patients received a nitrous oxide–opioid–barbiturate anesthetic so that the complicating effects of the presence of volatile agents at the neuromuscular junction could be avoided.

As others have reported, we found that neostigmine significantly decreased but did not abolish plasma cholinesterase activity. Neostigmine's effect on plasma cholinesterase activity was profound and prolonged. Almost 90 min after the administration of neostigmine, plasma cholinesterase activity had not yet recovered to 50% of baseline levels. It is likely that because of neostigmine's inhibition of plasma cholinesterase activity, the trans-trans isomer of mivacurium did not disappear as quickly from the plasma in patients treated with the anticholinesterase. Certainly, plasma cholinesterase activity is an important determinant of the pharmacodynamic behavior of mivacurium. Mivacurium infusion rates required to maintain a stable depth of neuromuscular block have been reported to be related to patients' plasma cholinesterase activity. In patients who are homozygous for atypical plasma cholinesterase, the duration of action is markedly prolonged as the relaxant is no longer actively metabolized and likely depends nearly entirely on renal and hepatic mechanisms of elimination from the plasma. Because of neostigmine's effect on plasma cholinesterase activity and because the clear-

Fig. 1. Individual plasma-concentration time curves for the cis-trans and the trans-trans isomers of mivacurium in patients after discontinuation of a mivacurium infusion. Breaks in the lines are a result of missing data points because of difficulty obtaining the plasma sample from the venous catheter. One patient in the spontaneous recovery group (patient #5) was eliminated because of injection into the mivacurium-containing intravenous line at the time of discontinuation of the infusion. The plasma concentration reported at 0 min is the baseline plasma concentration during the infusion.
Table 3. Plasma Concentration (ng/ml) of the cis-trans and trans-trans Isomers of Mivacurium after Discontinuation of an Infusion

<table>
<thead>
<tr>
<th>Time after Discontinuing Infusion (min)</th>
<th>Cis-trans</th>
<th>Trans-trans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neostigmine</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>Baseline</td>
<td>24.8 ± 9.1</td>
<td>23.9 ± 5.3</td>
</tr>
<tr>
<td>1</td>
<td>18.3 ± 7.8</td>
<td>18.5 ± 7.1</td>
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<tr>
<td>1.5</td>
<td>16.2 ± 11.2</td>
<td>15.8 ± 6.0</td>
</tr>
<tr>
<td>2</td>
<td>12.7 ± 7.5</td>
<td>11.2 ± 4.2</td>
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<tr>
<td>3</td>
<td>11.4 ± 7.9</td>
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<td>4</td>
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<td>6</td>
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<td>6.0 ± 5.3</td>
</tr>
<tr>
<td>8</td>
<td>5.1 ± 5.7</td>
<td>5.0 ± 5.6</td>
</tr>
<tr>
<td>10</td>
<td>5.0 ± 7.3</td>
<td>3.4 ± 6.1</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* P < 0.05 versus the spontaneous recovery group at the same time.
† P < 0.001 versus the spontaneous recovery group at the same time.

ance of the cis-trans and trans-trans isomers of mivacurium is related to plasma cholinesterase activity, had the anticholinesterase been administered at even more profound depth of neuromuscular block, it is likely that recovery may have been prolonged.

One might wonder why only the plasma concentrations of the trans-trans isomer and not those of the cis-trans isomer were significantly affected by the administration of neostigmine. This may be related to the size of our study population. As can be seen in table 3, there is a trend for the plasma concentrations of the cis-trans isomer to be higher in the neostigmine group. These differences in plasma concentrations, however, never achieved statistical significance. This same trend is seen in figure 1. At 4 min the isomer was detected in only four of seven patients in the spontaneous recovery group and in seven of eight patients in the neostigmine-treated group. If the number of patients studied had been greater, these trends might have achieved statistical significance.

Why, because we detected higher concentrations of the trans-trans isomer of mivacurium in the plasma of patients receiving neostigmine, did we not see a delay in recovery of neuromuscular function in this same patient population? A possible explanation is that neostigmine was not administered until 1 min after the discontinuation of the mivacurium infusion, allowing for substantial clearance of the potent isomers of mivacurium before the administration of the anticholinesterase. By the time that neostigmine had its peak effect on plasma cholinesterase activity, 2 min after its administration, 3 min or approximately two elimination half-lives of the active isomers had passed since discontinuation of the infusion. By that time, plasma concentrations of the cis-trans and trans-trans isomers of mivacurium had already decreased to the lower limit of detection of our assay. Such

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Fig. 3. Plasma cholinesterase activity (expressed as a percentage of baseline) over time after discontinuation of a 90-min mivacurium infusion and administration of neostigmine. Solid circles = the results from the spontaneous recovery group; open circles = those from the neostigmine group. At time zero, both groups have plasma cholinesterase activity at 100% of baseline. Plasma cholinesterase activity was decreased significantly to 7% of baseline values 2 min after discontinuation of the infusion and had increased to only 45% of baseline values 90 min after discontinuation of the infusion (89 min after administration of anticholinesterase).

Low plasma concentrations would have little, if any, clinical effect at the neuromuscular junction. If the same study had been conducted after discontinuation of higher infusion rates so that patients were 100% blocked or even during maintenance of a continuous infusion, as previously reported, we may well have observed a difference in the recovery profiles of the two patient study groups.

Effective antagonism of residual mivacurium-induced neuromuscular block with neostigmine occurs because increased amounts of acetylcholine are accumulated at the neuromuscular junction. On the basis of the results of this study, neostigmine can be used to antagonize residual mivacurium-induced neuromuscular block. As with other relaxants, however, pharmacologic antagonism of profound neuromuscular block (100% twitch inhibition) is not likely to be possible. Further, in the case of mivacurium, this may be particularly unwise, because slowing of metabolism of the drug while high concentrations of mivacurium are still circulating tends to oppose antagonism of the competitive neuromuscular block.

References


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