Early neuromuscular recovery characteristics following administration of mivacurium plus vecuronium

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Purpose: *This study was designed to describe the early recovery characteristics, as well as the speed of onset of neuromuscular block, after a combination of mivacurium and vecuronium.*

Methods: *In this controlled, randomized study, 30 consenting ASA I–III patients were assigned to three treatment groups. The "2M2V" group received twice the dose necessary to cause 95% depression of the evoked twitch response (2 × ED_{95}) of mivacurium (0.15 mg·kg^{-1}) plus 2 × ED_{95} of vecuronium (0.1 mg·kg^{-1}); the "2V" group received 2 × ED_{95} of vecuronium; and the "4V" group received 4 × ED_{95} of vecuronium. Evoked neuromuscular responses of the adductor pollicis were assessed with an adductor pollicis force transducer. The time until maximum block and times to 10% and 25% recovery (T_{10} and T_{25}) in each group were expressed as mean ± standard deviation and compared using ANOVA.*

Results: *Onset of block in the 2M2V group was 27% faster than in the 2V group (2.0 ± 0.6 vs. 2.7 ± 0.8 min respectively, P < 0.05) and was similar to the 4V group (1.95 ± 0.3 min, P = NS). The times until 10% recovery were similar in the 2M2V and 4V groups (59.9 ± 12 vs 68.2 ± 25 min, P = NS) and were slower than in the 2V group (37.2 ± 9 min, P < 0.05). Between T_{10} and T_{25}, recovery after 2M2V resembled that after 2V (6.7 ± 3 vs 5.7 ± 1 min, P = NS) and was faster than after 4V (10.9 ± 7 min, P < 0.05).*

Conclusions: *When 2 × ED_{95} of mivacurium is added to 2 × ED_{95} of an intermediate or long-acting relaxant, recovery after T_{10} will proceed as if one had administered the longer-acting agent alone.*

Objectif: *Décrire les caractéristiques de la curarisation initiale et de la décurarisation après l'administration du mivacurium associé au vécuronium.*

Méthodes: *Au cours de cette étude contrôlée aléatoire, 30 adultes consentants ASA I–III ont été répartis en trois groupes. Le groupe 2M2V a reçu deux fois la dose (2 × ED_{95}) de mivacurium (0,15 mg·kg^{-1}) nécessaire pour causer une dépression de 95% de la réponse au twitch plus 2 × ED_{95} de vécuronium (0,1 mg·kg^{-1}), le groupe 2V a reçu 2 × ED_{95} de vécuronium, et le groupe 4V, 4 × ED_{95} de vécuronium. Les réponses évoquées au niveau de l'adducteur du pouce ont été évaluées à l'aide d'un transducteur. Les temps nécessaires à une curarisation maximale et à 10% et 25% de décurarisation (T_{10} et T_{25}) dans chaque groupe ont été exprimés en moyenne ± écart-type et comparés avec ANOVA.*

Résultats: *Le début de la curarisation dans le groupe 2M2V a été de 27% plus rapide que dans le groupe 2V (respectivement 2,0 ± 0,6 vs 2,7 ± 0,8 min, P < 0,05) et identique au groupe 4V (1,95 ± 0,3 min, P = NS). Le temps nécessaire à 10% de décurarisation a été identique dans les groupes 2M2V et 4V (59 ± 0,3 vs 68 ± 25 min, P = NS) et était plus prolongé que dans le groupe 2V (37,2 ± 0 min, P < 0,05). La décurarisation entre T_{10} et T_{25} était identique après 2M2V et 2V (6,7 vs 5,7 ± 1 min, P = NS) et était plus rapide après 4V (10,9 ± 7 min, P < 0,05).*

Conclusion: *Quand le mivacurium 2 × ED_{95} est ajouté à ≥ 2 × ED_{95} d'un relaxant intermédiaire ou de longue durée, la décurarisation après T_{10} a les mêmes caractéristiques qu'un agent de longue durée administré seul.*

Key words

MONITORING: neuromuscular block: onset, recovery;
NEUROMUSCULAR RELAXANTS: vecuronium, mivacurium, combination.

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Although large bolus doses of mivacurium are not well-suited for rapid-sequence intubation because of their

TABLE Results

Group	*2M2V*	*2V*	*4V*
Onset (min)	1.98 ± 0.6 (1.2–2.8)	2.73 ± 0.8 (1.6–4.4)*	1.80 ± 0.3 (1.4–2.4)
T_{10} (min)	54.9 ± 12 (40.3–77.0)	37.2 ± 9 (21.2–57.3)*	69.5 ± 23 (36.3–109.9)
T_{25} (min)	61.5 ± 14 (43.8–89.3)	42.9 ± 10 (26.3–63.8)*	80.0 ± 29 (40.7–135.1)*
T_{10-25} (min)	6.65 ±3 (2.8–12.2)	5.72 ± 1 (4.1–7.6)	10.45 ± 6 (4.0–25.3)*

Data are expressed as mean ± standard deviation (range).
*$P < 0.05$ for difference between 2V or 4V group vs. 2M2V group.

histamine-releasing potential,[1] a moderate dose of mivacurium may prove to be a valuable component of combination therapy. Recent reports have indicated that combinations of mivacurium with vecuronium[2] or rocuronium[3] provide depth of block[2,3] and rate of onset[3] as effectively as, or more effectively than, an equivalent dose of either agent alone. Perhaps more importantly, because of its rapid and unique metabolism,[4–6] the use of mivacurium in combination with another agent may have minimal effect on the total duration of block. It was reported recently that a combination of a 1 × ED_{95} dose of mivacurium (i.e., the dose that depresses adductor pollicis twitch response by an average of 95%) plus 1 × ED_{95} of rocuronium caused neuromuscular block with a duration that was intermediate between that produced by 1 × and 2 × ED_{95} of rocuronium alone. The addition of 1 × ED_{95} of mivacurium had slowed recovery by 20 min. This 20-min prolongation was assessed by the time of recovery of twitch height to 25% of baseline (the first time-point reported). There was no difference in recovery rates beyond this point.[3]

The times when twitch height returns to 10% and 25% of baseline (T_{10} and T_{25}) are important time-points during recovery. First, the response to single twitch and the first response to train-of-four (TOF) stimulation typically became detectable by visual and tactile assessment once recovery reaches T_{10}. Subsequent recovery from neuromuscular block tends to proceed linearly, leading to the reliance upon the T_{10-25} and/or T_{25-75} recovery indices for comparison of drug regimens. Second, from a clinical standpoint, T_{10} represents an important time for decisions regarding either block supplementation or planning spontaneous recovery from and antagonism of nondepolarizing block.[7–10] We therefore elected to distinguish recovery before T_{10} from recovery between T_{10} and T_{25} in the present assessment of combination therapy with mivacurium plus vecuronium. We postulated that the early recovery period after a combination of 2 × ED_{95} of mivacurium and 2 × ED_{95} of vecuronium would resemble that obtained after a higher dose of vecuronium (4 × ED_{95}), while the recovery between T_{10} and T_{25} would have a time course similar to that after 2 × ED_{95} of vecuronium alone.

Methods

With institutional Review Board approval, informed written consent was obtained from 30 ASA I to III patients. After administration of 0–2 mg midazolam and 50–250 μg fentanyl *iv*, general anaesthesia was induced with thiopentone 2–3 mg·kg^{-1} *iv* and after loss of consciousness, the lungs were ventilated by mask with 70% nitrous oxide in oxygen. Neuromuscular function was measured in response to ulnar nerve supramaximal square-wave TOF stimulation at 12-sec intervals with an adductor pollicis force transduction monitor. After attainment of a stable baseline neuromuscular response, patients were randomly assigned to receive a rapid *iv* bolus of either: (1) mivacurium 0.15 mg·kg^{-1} plus vecuronium 0.1 mg·kg^{-1} (approximately 2 × ED_{95} of each drug, "2M2V" group); (2) vecuronium 0.1 mg·kg^{-1} alone ("2V"); or (3) vecuronium 0.2 mg·kg^{-1} alone ("4V"). Although clinically relevant histamine release following administration of 2 × ED_{95} of mivacurium is unlikely,[1,11] we observed all patients after administration of relaxant for facial flushing and changes in heart rate. Responses to TOF stimulation were recorded throughout the study period and the height of the first twitch of TOF was expressed as a percentage of its pre-relaxant baseline counterpart. After attainment of maximum block, the trachea was intubated and isoflurane 1.0–1.5% end-tidal concentration was added to the anaesthetic regimen and maintained throughout the study.

Evoked responses in the three patient groups were compared during onset with respect to the time from end of injection until maximum twitch depression and during recovery with respect to T_{10}, T_{25}, and the T_{10-25}. Data were analyzed with one-way analysis of variance (ANOVA) and Newman-Kuels multiple comparison tests. Statistical significance was defined as $P < 0.05$.

Results

There were no differences among the three patient groups with regard to age, weight or height. As shown in the Table, onset in the 2M2V group was 27% faster than in the 2V group ($P < 0.05$) and similar to that in the 4V group (P = NS).

No patient in any of the groups had visible flushing between the administration of relaxant and the time of intubation. All patients attained 100% neuromuscular block.

The effect of combining 2 × ED_{95} of mivacurium and 2 × ED_{95} of vecuronium on recovery prior to T_{10} differed from the effect on recovery after T_{10}. Before T_{10}, the rate of recovery in the 2M2V group was similar to that in the 4V group, and slower than in the 2V group. Between T_{10} and T_{25}, the rate of recovery was similar in the 2M2V and 2V groups (P = NS), and faster than in the 4V group ($P < 0.05$).

Discussion

Although we have witnessed the arrival of nondepolarizing relaxants which approach the rapid onset of succinylcholine, we still lack a nondepolarizing agent which can produce onset and duration conditions comparable with those achieved by succinylcholine without potentially undesirable effects. The administration of a large dose of relaxant (i.e., >2 × ED_{95}), traditionally vecuronium and more recently rocuronium, is a popular method for accelerating the onset of intubating conditions. However, drugs which depend on organ elimination (e.g., steroidal derivatives such as vecuronium, rocuronium, and pancuronium) exhibit dose-related prolongation of recovery. Those with organ-independent elimination (e.g., benzylisoquinoliniums such as mivacurium and atracurium) do not exhibit equivalent accumulation and prolongation of duration, but often are associated with clinically relevant histamine release after doses greater than 2 × ED_{95}.[1,11] These limitations of "high-dose" therapy may be obviated by "combination" therapy.

The most interesting finding of the present investigation was that the clinical effect of mivacurium abated by T_{10}, such that T_{10-25} was nearly identical in the 2V and 2M2V groups. This finding is consistent with the relative rates of recovery when each drug is used alone.[4,12,13] Within 30 min after 2 × ED_{95} of mivacurium, twitch height typically returns to >95% of baseline.[4–6] Alternatively, at this time, twitch height typically has recovered to 10% of baseline after a 2 × ED_{95} dose of a relaxant of intermediate duration, and to a much lesser degree after a 4 × ED_{95} dose.[14] Based on the respective time-courses of mivacurium and vecuronium when they are given individually, it is not surprising that, when given in the present combination, the effect of mivacurium would become negligible by T_{10}. However, this remained to be confirmed, since return of twitch height does not necessarily indicate absence of mivacurium from the neuromuscular junction and nonspecific binding sites; nor does it preclude persistent pharmacodynamic or pharmacokinetic interactions between the remaining mivacurium and the longer acting agent, especially in light of the potentiation that has been reported between mivacurium and steroidal-based relaxants.[2,3]

The confirmation that the clinical effect of mivacurium is negligible beyond T_{10} is important for the management of patients who receive combination therapy with mivacurium and a longer acting agent. The return of twitch height to 10% of baseline typically is associated with the ability to detect the first one or two twitches in response to TOF stimulation by visual or tactile means.[9] It is at this stage of recovery that clinicians typically make decisions concerning supplementation with additional relaxant or reversal with an anticholinesterase. While anaesthetists often elect to reverse the block induced by a nondepolarizing agent of short or intermediate duration upon recovery of only the first TOF twitch, many would elect to wait longer during recovery from an agent of long duration. The increase in neuromuscular function induced by the reversal agent may not be sufficient without a significant degree of spontaneous recovery from the relaxant itself. Such recovery is slower not only for long-acting agents, but also for high doses of an agent of intermediate duration such as vecuronium (or rocuronium). The present data indicate that the addition of a 2 × ED_{95} equivalent of mivacurium rather than an additional 2 × ED_{95} of vecuronium (i.e., 2M2V vs 4V) appears to reduce such prolongation. Measuring time to T_{25} allows us to compare two early recovery variables: recovery rate from complete block until T_{10}, and recovery rate from T_{10} to T_{25}. Typically, decisions concerning the adequacy of surgical relaxation and the timing and dosing of antagonism are made during this interval. As previously discussed, effective surgical relaxation is suspect beyond T_{25}, so the decision to reinforce, antagonize, or allow continued spontaneous recovery often must be made before this time. Since the T_{10} to T_{25} recovery rates are similar in the 2M2V and 2V groups, it is very likely that clinical decisions made at this time will have comparable impact after these two regimens.

Certain decisions were made with respect to this protocol which have an impact on the interpretation of data and the potential need for future investigations. Since an inhalational agent typically is not administered before tracheal intubation in a rapid sequence setting (where high-dose regimens may be indicated), we withheld isoflurane until after maximum block had been obtained. However, an inhalational agent is commonly used thereafter, as was the case in the present study. In addition, since the present report focused upon a comparison of the different neuromuscular blocking regimens with respect to recovery between 0–10% and

10–25% of twitch height, we did not standardize treatment beyond 25% recovery. Although similar responses would be anticipated, it remains to be confirmed that the 2V and 2M2V regimens would respond similarly to reversal.

The third decision involved the evaluation of vecuronium. This agent is readily available, and the pharmacodynamic and pharmacokinetic aspects of recovery after this drug have been studied extensively. In addition, it is anticipated that generic preparations will be available in less than one year, and that frequent use of this agent is very likely to continue. While the data generated in the present study may be applicable to combinations of mivacurium and rocuronium, this remains to be confirmed.

In conclusion, the present findings confirm that the addition of 2 × ED_{95} of mivacurium to 2 × ED_{95} of vecuronium provides onset of neuromuscular block virtually as rapidly as 4 × ED_{95} of vecuronium alone, while exerting only a relatively brief effect on recovery. We conclude that when 2 × ED_{95} of mivacurium is administered in combination with a 2 × ED_{95} dose of a longer acting agent, in the absence of atypical block prolongation (e.g., due to plasma cholinesterase deficiency), then recovery beyond T_{10} should proceed as if 2 × ED_{95} of the longer agent had been administered alone. While we anticipate that pharmacological reversal likewise would resemble that after 2 × ED_{95} of the longer acting agent, this remains to be confirmed.

References

1 *Savarese JJ, Ali HH, Basta SJ, et al.* The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide-opiate-barbiturate anesthesia. Anesthesiology 1989; 70: 386–94.

2 *Jalkanen L, Meretoja OA, Taivainen T, Brandom BW, Dayal B.* Synergism between atracurium and mivacurium compared with that between vecuronium and mivacurium. Anesth Analg 1994; 79: 998–1002.

3 *Naguib M.* Neuromuscular effects of rocuronium bromide and mivacurium chloride administered alone and in combination. Anesthesiology 1994; 81: 388–95.

4 *Savarese JJ, Ali HH, Basta SJ, et al.* The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 1988; 68: 723–32.

5 *Cook DR, Stiller RL, Weakly JN, Chakravorti S, Brandom BW, Welch RM.* In vitro metabolism of mivacurium chloride (BW B1090U) and succinylcholine. Anesth Analg 1989; 68: 452–6.

6 *Cook DR, Freeman JA, Lai AA, et al.* Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. Br J Anaesth 1992; 69: 580–5.

7 *Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD.* Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. Br J Anaesth 1989; 63: 393–9.

8 *Kopman AF.* Tactile evaluation of train-of-four count as an indicator of reliability of antagonism of vecuronium- or atracurium-induced neuromuscular blockade. Anesthesiology 1991; 75: 588–93.

9 *Viby-Mogensen J.* Clinical assessment of neuromuscular transmission. Br J Anaesth 1982; 54: 209–23.

10 *Silverman DG, Bartkowski RR.* Pharmacokinetics and pharmacodynamics of nondepolarizing relaxants: maintenance and recovery. *In*: Silverman DG. (Ed.). Neuromuscular Block in Perioperative and Intensive Care. Philadelphia: J.B. Lippincott, 1994: 95–103.

11 *Choi WW, Mehta MP, Murray DJ, et al.* Neuromuscular and cardiovascular effects of mivacurium chloride in surgical patients receiving nitrous oxide-narcotic or nitrous oxide-isoflurane anaesthesia. Can J Anaesth 1989; 36: 641–50.

12 *Weber S, Brandom BW, Powers DM, et al.* Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide-isoflurane and nitrous oxide-narcotic anesthesia in adult surgical patients. Anesth Analg 1988; 67: 495–9.

13 *Beauvoir C, Peray P, Daures JP, Peschaud JL, D'Athis F.* Pharmacodynamics of vecuronium in patients with and without renal failure: a meta-analysis. Can J Anaesth 1993; 40: 696–702.

14 *Silverman DG, Mirakhur RK.* Intermediate-acting relaxants of the 1980s. *In*: Silverman DG. (Ed.). Neuromuscular Block in Perioperative and Intensive Care. Philadelphia: J.B. Lippincott, 1994: 184–99.