CLINICAL INVESTIGATION

Recovery of Neuromuscular Function after a Combination of Mivacurium and Rocuronium

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Purpose: The present study was undertaken to evaluate onset, and early and late recovery of neuromuscular block after a combination of mivacurium (M) and rocuronium (R). Methods: In this controlled, randomized study, 45 consenting ASA I-II patients were assigned to one of three treatment groups: 2•ED95 R alone (2R); 2•ED95 R plus 1•ED95 M (2R1M); or 2•ED95 R plus 2•ED95 M (2R2M). Neuromuscular monitoring of the ulnar nerve consisted of surface electrode stimulation and force transduction of the adductor pollicis muscle. Stable baseline stimulation (1 Hz, square-wave, supramaximal current) was established prior to relaxant administration and continued until 95 percent twitch height depression (onset). Thereafter, train-of-four stimulation every 10 seconds was used to record recovery data until 95 percent recovery (T95%). Data were analyzed using grouped t-tests, ANOVA, and Newman-Keuls multiple comparison tests. Significance was defined at the p < 0.05 level. Results: The addition of mivacurium to rocuronium did not accelerate onset of block. The combination prolonged the clinical duration (time to 5 percent recovery, T5%), but did not affect subsequent recovery parameters: T5% in the 2R1M and 2R2M groups were 100 percent and 118 percent longer than in the 2R group, respectively (p < 0.05); the T25% (early recovery) and T25-75% (linear recovery) indexes were similar in all three groups. Conclusions: The present study did not note an acceleration of block onset when mivacurium was added to rocuronium. The findings suggest that the addition of mivacurium (1-2•ED95) to rocuronium (2•ED95) prolongs the clinical duration of the longer-acting agent, rocuronium, but has no effect on the early or linear recovery indexes of rocuronium. Thus, although clinical duration is prolonged, recovery from the combination regimens proceeds as if no mivacurium had been added to rocuronium.

INTRODUCTION

Even after the introduction of rocuronium (R) into clinical practice, a major focus of research with neuromuscular blocking agents has been the achievement of rapid onset of muscle relaxation using nondepolarizing agents, without undue prolongation of clinical duration or deleterious hemodynamic side-effects. It has long been appreciated that onset of neuromuscular block can be accelerated by increasing the dose of relaxant [1, 2]. However,
high-dose therapy is associated with an increase in the frequency of unwanted side-effects, such as prolongation of block [3] and/or histamine release [4]. The introduction of rocuronium into clinical practice has enabled more rapid attainment of block using doses that minimize these unwanted side-effects. However, in most cases, it is difficult to achieve the rapid onset (and, equally important, the reliable muscle relaxation) that can be obtained with succinylcholine when one uses doses of rocuronium that do not cause prolonged block [5].

Several investigators have shown that nondepolarizing relaxants often work synergistically and that when drugs possessing different side-effect profiles are combined, they can achieve the desired effect without exacerbating individual drug side effects. Stout and collaborators [6] showed that the combination of mivacurium (M) and vecuronium provided a favorable profile with respect to onset and duration of block when compared to vecuronium alone. Naguib [7] and Stevens and colleagues [8] have demonstrated that the combination of mivacurium plus rocuronium could be of value for patients requiring rapid onset of intubating conditions for surgeries of relatively brief durations. The effects of the drug combination on the duration of action and recovery indices, however, were less clear.

The present study was undertaken to evaluate the effect of combining mivacurium with rocuronium, and specifically to evaluate block onset time (time from drug administration until decrease of the first twitch of the train-of-four [T1] to 5 percent of baseline), the clinical duration (time from drug administration until recovery of T1 to 5 percent of baseline twitch), the early recovery index (T5-25%), and the linear recovery index (T25-75%). We evaluated recovery before and after 5 percent recovery of the first T1, since this is the time when decisions are made with respect to either supplementing the neuromuscular block or planning to administer reversal agents. In such a context, it would be important to know if neuromuscular recovery would proceed as if rocuronium had been given alone, or whether its recovery profile would be affected by a persistent effect of the added mivacurium.

We hypothesized that the addition of mivacurium to rocuronium would accelerate the onset of neuromuscular block in proportion to the ED95 equivalents administered. Moreover, this acceleration of onset should be accomplished without undue prolongation of rocuronium, since recovery from mivacurium is much faster than that from rocuronium, and each drug possesses a different mode of metabolism.

METHODS

With Institutional Review Board approval, informed written consent was obtained from 45 patients who were then randomly assigned to one of three treatment groups: 1) R 0.6 mg·kg⁻¹ alone (2•ED95 R, [2R]); 2) R 0.6 mg·kg⁻¹ plus M 0.07 mg·kg⁻¹ (2•ED95 R plus 1•ED95 M, [2R1M]); or 3) R 0.6 mg·kg⁻¹ plus M 0.15 mg·kg⁻¹ (2•ED95 of each drug, [2R2M]). All patients were ASA Physical Status I-II, 18 to 70 years of age, and within 25 percent of ideal body weight; none had any physical condition or had received any medications known to interfere with neuromuscular transmission. Halogenated anesthetic agents were avoided.

Anesthesia was induced with thiopental 2-4 mg·kg⁻¹ or propofol 1-2 mg·kg⁻¹, midazolam 0.03 mg·kg⁻¹, fentanyl 2-5 μg·kg⁻¹ and was maintained with 70 percent N₂O in oxygen (O₂) plus supplemental fentanyl and/or propofol as required. End-tidal carbon dioxide concentration (E₉CO₂), O₂ saturation, non-invasive blood pressure, heart rate, and temperature...
were all stable and maintained within typical physiologic ranges throughout the study. Neuromuscular monitoring of the ulnar nerve consisted of neurostimulation via surface electrodes at the wrist and force transduction monitoring of the adductor pollicis muscle.

Data were recorded by an interfaced computer that provided a resolution for individual twitch responses of 2 mmHg. After induction of anesthesia and establishment of adequate mask ventilation, the randomly assigned relaxant regimen was administered by IV bolus over a 3-second period. Stable baseline stimulation (1 Hz, square-wave, supramaximal current) was established for 10 minutes prior to relaxant administration, and was continued until 95 percent twitch height depression (defined as block onset). Thereafter, train-of-four stimulation every 10 seconds was used to record recovery data, where the relative height of the first T1 was compared to the pre-relaxant control T1 value and was recorded at 10-second intervals until 5 percent, 25 percent, 75 percent and 95 percent recovery (T5%, T25%, T75% and T95%, respectively). Data were analyzed using grouped t-tests, analysis of variance (ANOVA), and Newman-Keuls multiple comparison tests with corrections for multiple comparisons. Statistical significance was defined as $p < 0.05$.

**RESULTS**

The patients in the three treatment groups were similar with respect to age, height, weight, and gender distribution. The data obtained for onset and recovery are listed in Table 1. The addition of either 1•ED95 or 2•ED95 of mivacurium to rocuronium did not accelerate onset. However, both combination regimens demonstrated that the addition of mivacurium to rocuronium prolonged the time to 5 percent recovery (T5%), but did not affect recovery thereafter: T5% in the 2R1M and 2R2M groups were 100 percent and 118 percent longer than in the 2R group, respectively ($p < 0.05$); the T5-25% and T25-75% recovery indexes were similar in all three groups (Table 2).

| Table 1. Times to Onset and Early and Late Recovery (Mean ± SD). |
|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Group | Onset (min) | T5% (min) | T25% (min) | T75% (min) | T95% (min) |
| 2R | 0.8 ± 0.2 | 21.9 ± 8 | 27.6 ± 9 | 36.1 ± 14 | 40.6 ± 16 |
| 2R1M | 1.0 ± 0.3 | 43.8 ± 8* | 51.0 ± 10* | 62.8 ± 12* | 66.9 ± 13* |
| 2R2M | 0.9 ± 0.2 | 47.8 ± 13* | 55.0 ± 16* | 66.7 ± 22* | 75.5 ± 28* |

*p < 0.05 vs. Group 2R values (ANOVA with Bonferroni adjustment for multiple comparisons). R, rocuronium; M, mivacurium; T, time to recovery

| Table 2. Early and Linear Recovery Indexes (Mean ± SD). |
|----------------|----------------|----------------|----------------|
| Group | T5-25% (min) | P | T25-75% (min) | P |
| 2R | 5.7 ± 3 | | 8.5 ± 6 | |
| 2R1M | 6.2 ± 3 | P = NS | 11.5 ± 4 | P = NS |
| 2R2M | 7.3 ± 4 | P = NS | 11.7 ± 7 | P = NS |

R, rocuronium; M, mivacurium; T, time to recovery.
DISCUSSION

Recent advances in the pharmacology of muscle relaxants have resulted in the availability of an unprecedented number of drugs. Their development has been spurred, no doubt, by the quest for the “perfect” muscle relaxant, one that has the rapid and reliable onset of succinylcholine without any of its untoward side-effects. To date, no nondepolarizing muscle blocker (NMB) developed for clinical use achieves this ideal profile. Hence, clinicians have taken other approaches to achieving the rapid onset of succinylcholine.

Two of the most popular methods are large-dose (greater than 3-4•ED₉₅) NMB therapy and combination therapy. While large doses of NMBs may achieve the goal of rapid onset, their use is limited by two undesirable effects. In the case of steroidal derivatives, which depend on organ elimination, prolongation of block may be problematic when large doses are used [3]. With large doses of agents with organ-independent elimination, such as the benzylisoquinolinium compounds, clinically significant histamine release may occur [4]. Combination NMB therapy has been developed in an attempt to solve the shortcomings associated with large-dose single-agent therapy: normal doses (i.e., doses that are not usually associated with systemic side effects) of steroidal and benzylisoquinolinium compounds may be combined to achieve a large total drug dose and hasten onset, without producing the undesirable effects of large doses of either of the two individual NMBs.

Vecuronium and mivacurium have been used for this purpose with some degree of success [6]. More recently, rocuronium has been used in combination therapy [7, 8]. By administering it with mivacurium, we attempted to exploit the advantages of each drug: rocuronium's rapid onset and mivacurium's organ-independent elimination and short duration of action. The interaction between rocuronium and mivacurium has been shown to be synergistic with regard to potency, with the ED₉₅ of the mixture being only 62 percent of the predicted value based on a purely additive interaction [7].

On initial examination, the most surprising finding of the current investigation was that onset times were similar for all three groups. The present study did not note the acceleration of onset that was associated with combinations of mivacurium plus vecuronium and mivacurium plus rocuronium in previous studies [6, 7-11]. This may be attributable to multiple factors: 1) the more rapid apparent onset of block associated with stimulation at 1 Hz (as in our current study), a rate that has been shown to accelerate onset [12]; 2) the potential additive effect of mivacurium may have been overshadowed not only by the relatively rapid rate of stimulation, but also by the time required for circulation of the drug and its delivery to the biophase; and 3) the concept of molecular load. The time of onset of NMB is directly proportional to the number of molecules that are delivered to the biophase. Acceleration of onset can be achieved by administration of a large total dose, a drug with low plasma protein binding (that leaves more unbound drug available), or a drug with low potency [13]. In the case of a drug with low potency, for any specific ED₉₅, multiple, a greater total number of (less potent) molecules are administered, leading to faster occupancy of the requisite number of postsynaptic receptors (and thus, faster onset of block). Potency thus partially accounts for the slow onset of highly potent doxacurium, for the intermediate onset duration of the moderately potent mivacurium and vecuronium, and for the relatively fast onset of the least potent agent, rocuronium. Thus, adding 1•ED₉₅ M to 1•ED₉₅ R (i.e., doubling the ED₉₅ administered) increases the total number of molecules by
CONCLUSION

This study showed that the addition of mivacurium to rocuronium did not accelerate onset of neuromuscular block, but did prolong the $T_{5\%}$ recovery without affecting subsequent (linear) recovery index. Our study also expands upon other investigations that have failed to show a clear dose/response relationship between onset times and combination ED$_{95}$ multiples (mivacurium plus rocuronium). If clinicians choose combination therapy with mivacurium plus rocuronium to achieve prolongation of relaxation while avoiding class-specific side effects, they can expect that, once $T_{5\%}$ has been attained, recovery should proceed normally.

We conclude that when 2•ED$_{95}$ of mivacurium is administered in combination with a 2•ED$_{95}$ dose of a longer acting agent (e.g., rocuronium), in the absence of atypical block prolongation (due to pseudocholinesterase deficiency), then recovery beyond $T_{5\%}$ should proceed as if 2•ED$_{95}$ rocuronium alone had been administered. This is consistent with mivacurium's brief duration of action [14], and indicates that after attainment of $T_{5\%}$, subsequent recovery from (and probably reversal of) neuromuscular block should proceed as if the patient received 2•ED$_{95}$ of rocuronium alone. The consistency of linear recovery (RI$_{25-75\%}$) in our study is consistent with that reported previously; similar results were reported by Naguib and colleagues [7, 11] and Fletcher and colleagues [10] who found that the addition of mivacurium to rocuronium did not change the linear recovery index significantly.

REFERENCES

1. Casson WR and Jones RM. Vecuronium induced neuromuscular blockade. The effect of increasing dose on speed of onset. Anaesthesia 1986;41:354-7.
2. Lennon RL, Olson RA, and Gronert GA. Atracurium or vecuronium for rapid sequence endotracheal intubation. Anesthesiology 1986;64:510-3.
3. Rorvik K, Husby P, Gramstad L, Vannes JS, Bitsch-Larsen L, and Koller ME. Comparison of large dose of vecuronium with pancuronium for prolonged neuromuscular blockade. Br J Anaesth 1988;61:180-5.
4. Scott RP, Savarese JJ, Basta SJ, Embree P, Ali HH, Sunder N, and Hoaglin DC. Clinical pharmacology of atracurium given in high dose. Br J Anaesth 1986;58:834-8.
5. Cooper RA, Mirakhur RK, and Maddineni VR. Neuromuscular effects of rocuronium bromide (Org 9426) during fentanyl and halothane anesthesia. Anaesthesia 1993;48:103-5.
6. Stout RG, Brull SJ, and Silverman DG. Early neuromuscular recovery characteristics following administration of mivacurium and vecuronium. Can J Anaesth 1996;43:358-61.
7. Naguib M. Neuromuscular effects of rocuronium bromide and mivacurium chloride administered alone and in combination. Anesthesiology 1994;81:388-95.
8. Stevens JB, Shephered JM, Vories PA, Walker SC, and Vescovo MV. A mixture of mivacurium and rocuronium is comparable in clinical onset to succinylcholine. J Clin Anesth 1996;8:486-90.
9. Jalkanen L, Meretoja OA, Taivainen T, Brandom BW, and Dayal B. Synergism between atracurium and mivacurium compared with that between vecuronium and mivacurium. Anesth Analg 1994;79:998-1002.
10. Fletcher JE, and Heard CM. The clinical effect of mixing different proportions of rocuronium and mivacurium. Paediatr Anaesth 2004;14:152-7.
11. Naguib M, Samarkandi AH, Ammar A, and Turkistani A. Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children. Br J Anaesth 1997;79:450-5.
12. Ali HH and Savarese JJ. Stimulus frequency and dose-response curve to d-tubocurarine in man. Anesthesiology 1980;52:36-9.
13. Kopman AF. Pancuronium, gallamine, and d-tubocurarine compared: is speed of onset inversely related to drug potency? Anesthesiology 1989;70:915-20.
14. Savarese JJ, Ali HH, Basta SJ, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). Anesthesiology 1988;68:723-32.