

Table 1. Times to Onset and Early and Late Recovery (Mean \pm SD).

Group	Onset (min)	T _{5percent} (min)	T _{25percent} (min)	T _{75percent} (min)	T _{95percent} (min)
2R	0.8 \pm 0.2	21.9 \pm 8	27.6 \pm 9	36.1 \pm 14	40.6 \pm 16
2R1M	1.0 \pm 0.3	43.8 \pm 8*	51.0 \pm 10*	62.8 \pm 12*	66.9 \pm 13*
2R2M	0.9 \pm 0.2	47.8 \pm 13*	55.0 \pm 16*	66.7 \pm 22*	75.5 \pm 28*

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

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 (T_{5percent}, T_{25percent}, T_{75percent} and

T_{95percent}, 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 $p < .05$.

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 (T_{5percent}), but did not affect recovery thereafter: T_{5 percent} in the 2R1M and 2R2M groups were 100 percent and 118 percent longer than in the 2R group, respectively ($p < 0.05$); the T_{5-25 percent} and T_{25-75 percent} recovery indices were similar in all three groups (Table 2).

Table 2. Early and Linear Recovery Indexes (Mean \pm SD).

Group	T _{5-25percent} (min)	P	T _{5-25percent} (min)	P
2R	5.7 \pm 3		8.5 \pm 6	
2R1M	6.2 \pm 3	P = NS	11.5 \pm 4	P = NS
2R2M	7.3 \pm 4	P = NS	11.7 \pm 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 $3\text{-}4 \cdot \text{ED}_{95}$) 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-inde-

pendent elimination and short duration of action. The interaction between rocuronium and mivacurium has been shown to be synergistic with regard to potency, with the ED_{50} 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 ED_{95} multiple, a greater total number of (less potent) molecules are administered, leading to faster occupancy of the requisite number of postsynaptic receptors (and thus, fast 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 $1 \cdot \text{ED}_{95}$ M to $1 \cdot \text{ED}_{95}$ R (i.e., doubling the $\text{ED}_{95 \text{ percent}}$ administered) increases the total number of molecules by

Table 3. Neuromuscular blocker.

Drug	Molecular Weight	ED ₉₅ (mg/kg)	No. Molecules ED ₉₅ /kg
Mivacurium	1100.18	0.075	4.10 x 10 ¹⁶
Vecuronium	637.74	0.05	4.72 x 10 ¹⁶
Rocuronium	609.7	0.3	2.96 x 10 ¹⁷

only 14 percent (Table 3). In fact, mivacurium's contribution to the total number of free NMB molecules is even less, since rocuronium is not highly bound to plasma proteins.

Other investigations of combination therapy recovery profiles have had limitations. One study only assessed the traditional recovery index between 25 percent and 75 percent of baseline [7], while another examined only early recovery, between 10 to 25 percent [6]. High resolution monitoring employed during our study facilitated delineation of early recovery, thereby enabling us to document that the addition to rocuronium of 1 and 2•ED₉₅ of mivacurium prolonged T_{5 percent} recovery by 22 and 26 minutes, respectively, but did not cause further prolongation of recovery; thus, recovery after T5 percent proceeds as if 2•ED₉₅ rocuronium alone had been administered. This is consistent with mivacurium's brief duration of action [14], and indicates that after attainment of T_{5 percent}, subsequent recovery from (and probably reversal of) neuromuscular block should proceed as if the patient received 2•ED₉₅ of ropivacaine alone. The consistency of linear recovery (RI_{25-75percent}) 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.

CONCLUSION

This study showed that the addition of mivacurium to rocuronium did not accelerate onset of neuromuscular block, but did prolong the T_{5 percent} recovery without affecting subsequent (linear) recovery indexes. Our study also expands upon other investigations that have failed to show a clear dose/response relationship between onset times and combination ED₉₅ 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 percent} has been attained, recovery should proceed normally.

We conclude that when 2•ED₉₅ of mivacurium is administered in combination with a 2•ED₉₅ 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 percent} should proceed as if 2•ED₉₅ of the longer-acting agent had been administered alone. While we anticipate that pharmacologic reversal likewise would resemble that after 2•ED₉₅ of the longer acting agent, this remains to be confirmed.

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