SHORT COMMUNICATION

Interaction of Mivacurium with Vecuronium or Succinylcholine: Isobolographic Analysis

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Introduction

Synergism between nondepolarising agents mivacurium and pancuronium has been observed in patients[1] and vecuronium potentiated mivacurium's action *in vivo*[2]. However, interactions between mivacurium and other blockers were also simply additive[3,4]. Depolarising agent succinylcholine intensified pancuronium[5] and vecuronium[6] block but also had no effect on mivacurium's action[7,8]. Thus combinations of neuromuscular blockers may produce either additive or synergistic effects. This study specifically examined interactions between mivacurium-vecuronium and mivacurium-succinylcholine *in vitro* using the rat phrenic nerve-hemidiaphragm muscle preparation.

Materials and Methods

Rat hemi-diaphragms with attached phrenic nerves were mounted in 37 ° C organ baths containing pH 7.4 Kreb's buffer[9]. Supramaximal electrical stimuli (0.1 Hz, 0.2 msec duration) were delivered to the nerve and paralysis-concentration curves were constructed for mivacurium (Mv), vecuronium (Vc) and succinylcholine (SCh) in three sets of eleven preparations to yield concentrations at 50% paralysis (EC_{50}), defined as one dose equivalent unit, after fit to sigmoid E_{max} (Hill) equations. Eight preparations were then used to generate three points on the isobole for Mv-Vc and Mv-SCh combinations in ratios of 1:1, 1:3 and 3:1 of their EC_{50}. For each interaction study, individual drugs were also used in 24 preparations with concentrations of 0.2, 0.4, 0.8, 1.2 and 1.6 of their EC_{50} to construct their concentration-response curves. EC_{50} estimates (± SEM) for each blocker were compared using ANOVA and Fisher's LSD test. Neuromuscular blocker interactions were assessed by constructing isobolograms[10] by plotting the fraction of EC_{50} of the single drugs on the dose unit co-ordinates together with the EC_{50} of the various blocker combinations in the chosen dose field. If the fraction of EC_{50} of a combination fell on the theoretical additive line, the effect of the drug mixture was additive, if points fell below the additive line, the interaction was synergistic and if the points fell above the line an antagonistic interaction was postulated. Single drug EC_{50} values were compared with the drug-drug EC_{50} values by unpaired t-test, $P<0.05$ was considered significant.

Results and Discussion

Mivacurium, vecuronium and succinylcholine concentrations at 50% paralysis (EC_{50}) were 3.26 ± 0.07, 3.01 ± 0.13 and 9.76 ± 0.52 μM respectively.

Mivacurium and vecuronium were equipotent but succinylcholine was one-third as potent as mivacurium and vecuronium ($P<0.001$).

Experimentally determined EC_{50} of a mivacurium-vecuronium combination at a dose ratio of 3:1 fell significantly below the corresponding theoretical additive point (Table 1), indicative of synergism between these two blockers at this dose ratio. Interactions of mivacurium and vecuronium at 1:1 and 1:3 dose ratios were simply additive (Table 1). EC_{50} ratios of mivacurium and succinylcholine at all three dose combinations did not deviate significantly from the corresponding theoretical additive points, indicating simple additive interactions between mivacurium and succinylcholine (Table 1).

Table 1 Fraction of EC_{50} values for Mv-Vc and Mv-SCh combinations

Blocker Combination	Fraction of EC_{50}	
	Theoretical	Experimental
Mv-Vc (1:1)	1.03 ± 0.03	0.98 ± 0.05
Mv-Vc (1:3)	1.05 ± 0.04	0.94 ± 0.04
Mv-Vc (3:1)	1.02 ± 0.03	0.88 ± 0.03*
Mv-SCh (1:1)	1.00 ± 0.03	1.05 ± 0.04
Mv-SCh (1:3)	1.01 ± 0.03	1.04 ± 0.03
Mv-SCh (3:1)	1.01 ± 0.03	1.06 ± 0.04

Values are mean ± SEM; * $P< 0.05$ compared to theoretical additive value; n = 8 for each combination

A 3:1 dose ratio combination of mivacurium with vecuronium was synergistic but not at the 1:1 or 1:3 dose ratios. The synergism was, however, minor and unlikely to be clinically significant and may be due to binding at both pre- and post-synaptic sites at the neuromuscular junction[11]. This *in vitro* result is generally consistent with similar observations *in vivo* where combinations of structurally dissimilar neuromuscular blockers (e.g. vecuronium and mivacurium) were synergistic[1,2]. Interactions between mivacurium and succinylcholine, both ester drugs, but the former a depolarising agent and the latter a non-depolarising agent were simply additive at all three dose ratios studied.

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