NEUROMUSCULAR TRANSMISSION I

A772

TITLE: AUTONOMIC AND NEUROMUSCULAR EFFECTS OF MIVACURIUM AND ISOMERS IN CATS

AUTHORS: R. B. Maehr, B.S., M. R. Belmont, M.D., D. L. Wray, M.D., J. J. Savarese, M.D., W. B. Wastila, Ph.D.

AFFILIATION: Division of Pharmacology, Wellcome Research Laboratories, Burroughs Wellcome Co., Research Triangle Park, N.C. 27709 and Department of Anesthesiology, New York Hospital, Cornell Medical Center, New York, N.Y. 10021

INTRODUCTION: Mivacurium is a mixture of three stereoisomers: 1309U83 (trans-trans), 1333U83 (cis-trans), and 1217U84 (cis-cis). The former two isomers represent 95% of the mivacurium mixture. The autonomic and neuromuscular blocking (NMB) profiles of mivacurium and its three stereoisomers were evaluated in cats.

METHODS: ED_{50} values for inhibition of autonomic and neuromuscular function were determined in 20 anesthetized cats. The trachea was cannulated and ventilation controlled with room air. Heart rate and arterial blood pressure were recorded. Twitches of the left tibialis anterior were evoked via the stimulation of the peroneal nerve at 0.15Hz. The cut distal ends of the right preganglionic sympathetic trunk and the right vagus nerve were stimulated to elicit sympathetic (nictitating membrane contraction) and parasympathetic (vagal-induced bradycardia) responses. Dose-related response curves for inhibition of neuromuscular and autonomic function were constructed for each isomer. A triphasic blood pressure response, increase in heart rate, and contraction of the nictitating membrane were taken as an indication of histamine release.

RESULTS: The mean (± S.E.) ED_{95} NMB values for mivacurium, 1309U83, 1333U83, and 1217U84 were: 47 ± 3, 42 ± 3, 45 ± 3, and 592 ± 41 µg/kg, respectively. The total durations were: 12.5 ± 1.1, 13.1 ± 0.3, 11.3 ± 1.4, and 11.2 ± 1.3 min., respectively. Doses that produced 50% inhibition of neuromuscular (NMB), parasympathetic (vagal), and sympathetic function are summarized in the Table. Mivacurium, 1309U83, and 1333U83 produced histamine-like effects at doses greater than 15x the ED_{95} NMB doses. Histamine-like effects were not observed after the administration of 1217U84 at doses as high as 2.0 mg/kg.

CONCLUSIONS: All three stereoisomers are short-acting NMB agents in cats. The ED_{95} NMB doses of 1309U83 and 1333U83 are not significantly different from each other or mivacurium. Compound 1217U84 is approximately 10x less potent than either of the other stereoisomers or mivacurium. Compounds 1309U83 and 1333U83 have high autonomic: neuromuscular dose ratios and most likely contribute equally to the pharmacological profile of mivacurium. Because 1217U84 is 10X less potent and only represents ~5% of mivacurium, it unlikely contributes in a significant way to the NMB profile of mivacurium.

	MIVACURIUM	1309U83	1333U83	1217U84
NMB ED_{50} (µg/kg)	36 ± 3	29 ± 8	32 ± 2	441 ± 28
VAGAL ED_{50} (µg/kg)	2000	1400	1900	2000
SYMPATHETIC ED_{50} (µg/kg)	>5120	>5120	>5120	>2000

A773

TITLE: COMPARATIVE PHARMACOLOGY OF MIVACURIUM ISOMERS IN CATS

AUTHORS: M. R. Belmont, M.D., D. L. Wray, M.D., R. B. Maehr, B.S., J. J. Savarese, M.D., W. B. Wastila, Ph.D.

AFFILIATION: Department of Anesthesiology, New York Hospital, Cornell Medical Center, New York, N.Y. 10021, and Division of Pharmacology, Wellcome Research Laboratories, Burroughs Wellcome Co., Research Triangle Park, N.C. 27709

INTRODUCTION: Mivacurium, a new non-depolarizing neuromuscular blocking (NMB) agent of short duration[1], is composed of three isomers. Previous work has established that 95% of the drug is made up of the two potent isomers 1309U83 and 1333U83. The remaining 5% is the 10X less potent isomer 1217U84. Since 1309U83 and 1333U83 are most likely responsible for the NMB activity of mivacurium it is important to characterize their relative potencies and NMB profiles in comparison to mivacurium.

METHODS: Male cats weighing between 2.9-5.2 kg were anesthetized with alpha-chloralose (80 mg/kg) and pentobarbital (10 mg/kg) i.p. The trachea was cannulated and ventilation was controlled with room air. The right femoral vessels were cannulated for drug administration and for arterial blood pressure recording. Heart rate was recorded from the ECG. Square-wave stimuli were applied at supramaximal voltage to the left peroneal nerve at 0.15Hz and the evoked twitches of the tibialis anterior were recorded. NMB ED_{95} values were determined from eight cats. Groups of five cats randomly received 1309U83 or 1333U83 in each of three dosing paradigms: 1) doses to produce between 95% and 99% block; 2) 0.15 mg/kg (4xED_{95}); 3) continuous infusions for 60 min. to maintain 95%-99% NMB.

RESULTS: The ED_{95} NMB values (mean ± s.e.m.) for 1309U83 and 1333U83 were 0.042 ± 0.003 and 0.045 ± 0.003 mg/kg, respectively. The NMB profiles observed after the three dosing paradigms are shown in the table.

CONCLUSION: The comparable potencies and recovery rates for the isomers in three different dosing paradigms indicate that each isomer contributes equally to the NMB profile of mivacurium. The relatively small increase in duration (34% for 1309U83 and 49% for 1333U83) and the fast recovery rates observed with a large (≈ 400%) increase in dose suggest first order kinetics. The recovery rates after infusions illustrate the lack of cumulative effects.

REFERENCE: [1]Anesthesiology 68:723-732, 1988

Compound	Dose (mg/kg)	Onset (min.)	Duration* (min.)	Recovery Rates (min.) 25%-75%	5%-95%
1309U83	0.041 (± 0.002)	4.2 (± 0.1)	13.1 (± 0.3)	3.2 (± 0.1)	7.5 (± 0.5)
	0.165	0.7 (± 0.1)	17.5 (± 1.0)	2.5 (± 0.1)	5.9 (± 0.4)
	0.0060 mg/kg/min (± 0.0005)			1.8 (± 0.4)	4.1 (± 0.3)
1333U83	0.045 (± 0.002)	4.2 (± 0.3)	11.3 (± 1.4)	2.4 (± 0.4)	6.4 (± 1.2)
	0.165	0.8 (± 0.1)	16.8 (± 0.6)	2.5 (± 0.2)	5.7 (± 0.4)
	0.0053 mg/kg/min (± 0.0006)			2.0 (± 0.1)	4.6 (± 0.2)

values = mean (± s.e.m.) n = 5 in all groups

*Duration = time of injection to 95% recovery