

Title : BW444U: AN INTERMEDIATE-DURATION NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENT WITH SIGNIFICANT LACK OF CARDIOVASCULAR AND AUTONOMIC EFFECT

Authors : John J. Savarese, M.D. and William B. Wastila, Ph.D.

Affiliation: Anesthesia Laboratories, Harvard Medical School at Massachusetts General Hospital, Boston, Massachusetts, and Department of Pharmacology, Wellcome Research Laboratories, Burroughs Wellcome Company, Research Triangle Park, North Carolina

Introduction. Compound BW444U is a non-depolarizing ester neuromuscular blocking agent which has a duration of action in rhesus monkeys intermediate between d-tubocurarine and succinylcholine (15-18 minutes at the ED95 for neuromuscular blockade) vs 3-5 minutes for succinylcholine and 35-50 minutes for d-tubocurarine. The compound is slowly hydrolyzed by human plasma cholinesterase. The autonomic effects of 444U in cats and the cardiovascular effects in rhesus monkeys are widely separated from the neuromuscular blocking action. The data have been compared with results previously obtained for d-tubocurarine¹, metocurine¹, and pancuronium.²

Methods. Eight cats were anesthetized with alpha-chloralose (80 mg/kg) and pentobarbital (10 mg/kg) i.p. The trachea was cannulated and the animals were ventilated at 12-15 ml/kg, 18-20 breaths per minute. Heart rate, EKG, and arterial pressure were recorded. Twitches of the tibialis anterior muscle were evoked via the peroneal nerve at 0.15 Hz. Trains of square waves (20 Hz for 10 seconds, repeated every 4-5 minutes) were applied simultaneously to the severed distal ends of the preganglionic portions of the right cervical sympathetic trunk and vagus nerve to elicit nictitating membrane contraction (sympathetic ganglionic) and vagal-induced bradycardia (parasympathetic) responses. Dose-response curves for inhibition of neuromuscular, vagal (parasympathetic) and sympathetic (ganglionic) function were constructed. Occurrence of the delayed depressor response and its inhibition by a combination of H₁ and H₂ receptor antagonists was taken as evidence of histamine release.¹ The dose-ratios of ED95 for neuromuscular blockade vs ED50 for sympathetic ganglionic and vagal block and for histamine release were determined.¹

Five rhesus monkeys weighing 5-9 kg were anesthetized with thiopental (35-40 mg/kg) i.m. The trachea was intubated and anesthesia was maintained with N₂O/O₂ (3L:1L) and halothane, 0.25-0.75% inspired. Heart rate, Ekg, and arterial pressure were recorded. Tibialis anterior twitch was evoked via the peroneal nerve at 0.15 Hz.

Animal and muscle temperature was maintained at 35-38° C.

Results. Inhibition of Autonomic and Neuromuscular Function (all dosage mg/kg)

	444U	dtc ¹	Meto-curine ¹	Pancuro-nium ²
ED95 (NM block)	0.065	0.35	0.025	0.022
ED50 (gang. block)	11.9	1.35	4.40	23.0
ED50 (vagal block)	1.87	0.29	0.85	0.20
ED50 (hist. release)	1.02	0.40	0.88	none

Dose-Ratios	444U	dtc	Meto-curine	Pancuro-nium
ED50 (gang. block)	183.1	3.86	176.0	1045.0
ED95 (NM block)				
ED50 (vagal block)	28.8	0.83	34.0	9.1
ED95 (NM block)				
ED50 (hist. release)	15.7	1.14	35.2	none
ED95 (NM block)				

The vagolytic effect of 444U, based on inhibition of the bradycardic response to methacholine (20 ug/kg i.v.) appeared to occur both at ganglionic and postganglionic sites, with the postganglionic (muscarinic receptor) block predominating.

Results. Cardiovascular Effects in Monkeys (all dosage mg/kg; all values \pm SE; * = $p < .05$)

Dose 444U	Neuromuscular Block (%)	Heart Rate (% Control)	Mean Art. Press. (% Control)
0.042	12.7 \pm 8.7	101.0 \pm 1.7	100.3 \pm 1.7
0.085	64.7 \pm 15.8	101.2 \pm 2.0	99.3 \pm 1.6
0.17	98.7 \pm 1.6	99.7 \pm 2.4	99.7 \pm 1.2
0.34	100	92.8 \pm 4.1	98.5 \pm 1.2
0.68	100	77.8 \pm 5.4*	104.5 \pm 3.3

Conclusion. BW444U is a potent intermediate-duration nondepolarizing neuromuscular blocking agent. Its histamine-releasing property and autonomic-neuromuscular profile is comparable to that of metocurine in the cat. Cardiovascular effects in the rhesus monkey show no significant change at up to five times the ED95 for neuromuscular blockade.

References.

1. Savarese JJ: The autonomic margins of safety of metocurine and d-tubocurarine in the cat. Anesthesiology 50:40-46, 1979
2. Savarese JJ, Ali HH: The autonomic margin of safety of alcuronium and pancuronium. Abstracts of Scientific Papers, IARS Meeting, Miami, 1977