Title : AUTONOMIC/NEUROMUSCULAR DOSE-RATIOS AND HEMODYNAMIC EFFECTS OF BW785U, A SHORT-ACTING NONDEPOLARIZING ESTER NEUROMUSCULAR BLOCKING AGENT

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Introduction. The clinical need for a short-acting nondepolarizing neuromuscular blocking agent may be satisfied only if, in addition to brevity of action, the new drug has acceptable cardiovascular effects. Compound BW785U , a short-acting nondepolarizing ester, has demonstrated considerable separation of its neuromuscular blocking action from any important autonomic/hemodynamic side effects in animal studies. Comparisons have been made with data previously obtained for d-tubocurarine[1], metocurine[1], and pancuronium.[2]

Methods. Dose-ratios for inhibition of autonomic vs neuromuscular function were determined in ten cats given α-chloralose and pentobarbital (80 mg/kg + 10 mg/kg) i.p. The trachea was cannulated and ventilation controlled at 12-15 ml/kg, 18-20 breaths per minute. EKG, heart rate, and arterial pressure were recorded. Twitches of the right tibialis anterior were evoked via the peroneal nerve at 0.15 Hz. The cut distal ends of the preganglionic portion of the right sympathetic trunk and the right vagus nerve were stimulated simultaneously with trains of square waves (20 Hz for 10 seconds, repeated every 4-5 minutes) to elicit sympathetic ganglionic (nictitating membrane contraction) and parasympathetic (vagal-induced bradycardia) responses. Dose-response curves for inhibition of neuromuscular, vagal (parasympathetic), and sympathetic ganglionic function were constructed. Occurrence of the triphasic "delayed depressor response", and its inhibition by a combination of H_1 and H_2 receptor antagonists, was interpreted as evidence of histamine release.[1] Dose-ratios (ED50/ED95) for histamine release and autonomic vs neuromuscular block were calculated.

Seven mongrel dogs weighing 8-15 kg were anesthetized with pentobarbital (30 mg/kg i.v.). Three of the animals were chronically instrumented with indwelling electromagnetic flow probes placed on the ascending aorta and with cannulae in the left carotid artery. The trachea was intubated and the animals were ventilated with room air (12-15 ml/kg, 20 breaths per minute). Arterial pressure, heart rate, and EKG were recorded. Electromagnetic flow signals were integrated and summated over time to yield cardiac output. Body temperature was maintained at 37-38° C. BW785U was administered as a rapid bolus I.V. at the ED95-100 (0.05 mg/kg) and the changes in measured parameters noted. Changes in peripheral resistance were calculated. Dosage of BW785U was doubled every 15 minutes up to 0.20 mg/kg or cumulative 7 x ED95-100 in chronically instrumented dogs and up to 30 x ED95-100 in acute experiments.

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

	785U	dtc[1]	Meto-curine[1]	Pancuro-nium[2]
ED95 (NM block)	0.15	0.35	0.025	0.022
ED50 (gang. block)	18.0	1.35	4.40	23.0
ED50 (vagal block)	5.1	0.29	0.85	0.20
ED50 (hist. release)	0.90	0.40	0.88	none

The vagal-blocking property of 785U appeared to occur principally at ganglia, as judged by lack of inhibition of methacholine-induced bradycardia.

Dose-Ratios	785U	dtc	Meto-curine	Pancuro-nium
ED50 (gang. block) / ED95 (NM block)	120.0	3.86	176.0	1045.0
ED50 (vagal block) / ED95 (NM block)	34.0	0.83	34.0	9.1
ED50 (hist. release) / ED95 (NM block)	6.0	1.14	35.2	none

Results. Hemodynamic Effects

No significant changes in heart rate, arterial pressure, or cardiac output were noted in chronically-instrumented or acutely-experimented animals at up to a cumulative dosage of 0.35 mg/kg (7 x ED95-100). Dosage was increased to 30 x ED95-100 in acute animals (cumulative dosage 1.5 mg/kg). After the final dose increment (0.8 mg/kg or 16 x ED95-100), the maximum mean arterial pressure and heart rate changes observed were -34 ± 14% and +29 ± 9% respectively ($P < .05$).

Conclusions. BW785U shows a wide separation of its autonomic effects from its neuromuscular blocking action. Release of histamine may occur at doses higher than six times the ED95 in the cat. Cardiovascular changes in dogs at thirty times fully paralyzing dosage may be due to this mechanism. The autonomic vs neuromuscular profile in cats of BW785U is most like that of metocurine, i.e. it is an extremely weak ganglion blocker and it does not have a muscarinic vagolytic effect.

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