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Title : CLINICAL NEUROMUSCULAR PHARMACOLOGY OF BW785U, AN ULTRA-SHORT-ACTING NONDEPOLARIZING ESTER NEUROMUSCULAR BLOCKING AGENT

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Introduction. BW785U, a nondepolarizing ester neuromuscular blocking agent rapidly hydrolyzed by human plasma cholinesterase, has shown a brief duration of action in experimental animals. The compound was judged worthy of clinical evaluation on this basis and because its side effects were not prominent within the neuromuscular blocking dose range.[1,2] A study of the clinical pharmacology of BW785U in human subjects has been carried out and is reported herein.

Methods. The planned protocol was approved by the hospital's Human Studies Committee. Signed informed consent was obtained from all 20 subjects who were of nonchildbearing potential and ranged in age from 18-45 years and in weight from 55-90 kg. No premedication was given. Anesthesia was induced with thiopental (4-6 mg/kg) and fentanyl (1.5-2.0 µg/kg) and maintained with nitrous oxide and oxygen (4L/2L) by mask. Further increments of thiopental and fentanyl were given as necessary. End-tidal and/or arterial PCO_2 was maintained in the range 45-50 torr by assisted ventilation. Arterial pressure was measured from a 20 gauge cannula in a radial artery. EKG (lead II) was monitored and the R-wave spike was used to trigger a cardiotachometer. Twitch tension of the thumb was evoked at 0.15 Hz by supramaximal square-wave stimuli applied to the ulnar nerve at the wrist through 22 gauge steel needles. Recordings were made via appropriate transducers on a Grass model 7 polygraph.

BW785U was given as a 15-45 second bolus intravenously to 9 subjects. Each received 3-4 graded doses of BW785U at approximately ½-hour intervals. Fifteen minutes was allowed between 100 percent twitch recovery and subsequent dosage. In 11 additional subjects, BW785U was administered continuously via an IMED pump for 1-3 hours, during which time neuromuscular blockade was monitored using train-of-four stimulation (2 Hz for 2 seconds, repeated every 10 seconds). The block was maintained at 75-95 percent twitch inhibition (train-of-four count 1-3) during the entire infusion.

Results. BW785U produced typical nondepolarizing block (absence of fasciculation, fade of train-of-four and tetanic response, and marked posttetanic twitch facilitation) of rapid onset and very short duration (table I). The block was readily antagonized by neostigmine or edrophonium.

Table I

Dose BW785U (mg/kg)	% Twitch Block ± SE	Onset (min.) to Peak Effect	Duration (min. ± SE) Inj-95% Recovery
0.4 (n=4)	55.8 ± 3.8	1.75 ± 0.2	6.9 ± 0.8
0.6 (n=8)	83.3 ± 8.4	1.75 ± 0.1	10.8 ± 1.7
1.2 (n=5)	99.6 ± 0.3	1.51 ± 0.2	16.4 ± 2.0

After infusions of 785U lasting 1-3 hours, spontaneous recovery of neuromuscular function was very rapid and was not related to the duration of the infusion. An initial infusion rate of 0.4 mg/kg/minute produced 100 percent twitch inhibition within 2 minutes. The infusion rate necessary for maintenance of 75-95 percent twitch inhibition was in the range 0.05-0.10 mg/kg/min.

Table II: BW785U Infusion (n=11)

Onset (min. ± SE) to 100% Block at Infusion Rate of 0.4 mg/kg/min.	1.5 ± 0.1
Infusion Maintenance Rate (mg/kg/min. ± SE)	0.08 ± 0.01
Infusion Duration (min. ± SE)	93.0 ± 15.8
Recovery Time, 5 → 95% Twitch Height (min. ± SE)	16.0 ± 1.3

Conclusion. From the point of view of its neuromuscular blocking action, BW785U appears to possess ideal relaxant properties. It was found, however, during this initial study, that the compound possesses a stronger histamine-releasing property in man than it does in animals.[3] This side effect seems prominent enough to dissuade us from further clinical investigation of BW785U.

References.

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2. Wastila WB, Savarese JJ: Autonomic/neuromuscular dose-ratios and hemodynamic effects of BW785U, a short-acting nondepolarizing ester neuromuscular blocking agent. Abstracts of Scientific Papers, 1979 ASA Meeting, San Francisco. Anesthesiology 51:S278, 1979

3. Rosow CE, Basta SJ, Savarese JJ, Ali HH, Kniffen KJ, Moss J: BW785U: Correlation of cardiovascular effects with increases in plasma histamine. Abstracts of Scientific Papers, 1980 American Society of Anesthesiologists Annual Meeting, St. Louis.