Title : PHARMACOLOGY OF BW785U: A SHORT-ACTING NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENT

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Introduction. BW785U, a nondepolarizing ester neuromuscular blocking agent of short duration, may fill the existing clinical need for such a drug. Evaluation of BW785U in human subjects will be underway during the summer of 1979. The pharmacology of 785U has been studied in the cat and dog and in rhesus and cynomolgus monkeys. The potency and duration of action of 785U were compared with data for d-tubocurarine.

Methods. Cats were anesthetized with alpha-chloralose (80 mg/kg) and pentobarbital (10 mg/kg) i.p. Dogs were given chloralose (80 mg/kg) i.p. and morphine (2 mg/kg) s.c. Primate species received thiopental (35-40 mg/kg) i.m. followed by halothane (0.5-1.0% inspired), nitrous oxide (60%), and oxygen in a nonrebreathing system. In all animals, the trachea was intubated and ventilation was controlled at 12-15 ml/kg, 18-24 breaths per minute to maintain end-tidal PCO_2 at 3-4%. Animals not receiving inhalation anesthetics were ventilated with room air. The left femoral vessels were cannulated for drug administration and for recording of arterial pressure and heart rate. Square-wave stimuli were applied at supramaximal voltage to the right peroneal nerve at 0.15 Hz and the evoked twitches of the tibialis anterior were recorded. Tetanic (50 Hz for 5 seconds) and train-of-four (2 Hz for 2 seconds) stimulation was also applied when appropriate. Muscle and animal temperatures were maintained between 35° C. and 38° C.

Intracellular recordings of the effects of 785U on end-plate resting membrane potential, miniature end-plate potential, and evoked end-plate potentials were made in the frog sciatic nerve-sartorious preparation in vitro.[1]

Hydrolysis of 785U by human plasma ChE was measured in vitro. The I50's for inhibition of human plasma ChE and eel Acetyl ChE were determined.

Results. 785U is rapidly hydrolyzed by human plasma cholinesterase (3.27 μMol/hr vs 2.34 μMol/hr for succinylcholine). It does not inhibit pseudocholinesterase (I50 = 6.5×10^{-4} M/L for the human enzyme) or eel acetylcholinesterase (I50 = 1.5×10^{-3} M/L).

The neuromuscular blocking potency (ED95 for twitch inhibition) and duration of action of 785U (from injection to 95% twitch recovery) in various species is compared with data for d-tubocurarine in the following table (all dosages in mg/kg and duration in min.).

	785U		d-Tubocurarine	
Species	ED95	Duration	ED95	Duration
Cat	0.1 -0.2	7-10	0.2 -0.4	25-35
Dog	0.03-0.05	15-20	0.2 -0.3	30-40
Rhesus	0.3 -0.5	3- 5	0.15-0.2	35-50
Cynomolgus	0.4 -0.6	5- 7	0.15-0.2	35-50

Neuromuscular block by 785U in all species showed nondepolarizing characteristics: Fade of tetanus and train-of-four, posttetanic potentiation of the twitch, and antagonism by anticholinesterases, 4-aminopyridine, and depolarizing substances. 785U had no effect on resting membrane potential of frog muscle in vitro and blocked neurally-evoked end-plate potentials as well as depolarization produced by iontophoretically-applied acetylcholine.

One-hour infusions of 785U in cats and monkeys during which 90-95% twitch inhibition was maintained showed spontaneous recovery to control twitch height within less than five minutes after termination of the infusion.

Discussion. Extraordinarily rapid hydrolysis of 785U by human plasma ChE (50% faster than succinylcholine) suggests that its duration of action in man should be very short. Marked species differences in potency and duration of action of 785U are easily explained by variation in plasma cholinesterase activity: The duration is shortest and potency least in species known to possess a very active enzyme, e.g. monkeys, whereas potency is greatest and duration longest in species having an inactive enzyme, e.g. dogs.

References.

1. Wang c: Personal communication