Date:

Title: PREDICTION OF CLINICAL NEUROMUSCULAR ED95 OF BW785U FROM LOW DOSE STUDIES IN AWAKE VOLUNTEERS

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BW 785U, a short acting nondepolarizing ester neuromuscular blocking agent, is hydrolysed by human plasma cholinesterase. Its pharmacology and toxicology have been reported in experimental animals by Savarese et al and Wastilla et al (1979).

The clinical effects of BW785U were studied and compared in unmedicated awake and anesthetized volunteers at two stimulus frequencies (1.0 and 0.15 Hz). An attempt was made to predict the ED95 of the relaxant at a slow stimulus rate in anesthetized individuals. This dosage is adequate for laryngoscopy and endotracheal intubation with other nondepolarizing relaxants. Detailed informed consent was obtained from all volunteers. The study was approved by the Committee on Human Studies of our institution.

Methods. Eight ASA I adult volunteers (29-35 years) weighing 66-76 kg were divided into two groups. Group I consisted of four unmedicated awake volunteers. In Group II four volunteers were anesthetized with thiopental (3-4 mg/kg), 66% nitrous oxide in oxygen and (2 µg/kg) fentanyl. Additional thiopental and fentanyl were given as necessary. The mean total dosages were 6 mg/kg and 3.6 µg/kg respectively. Neuromuscular function was measured by recording evoked thumb adduction using Grass FT-10 transducers and a Grass polygraph. Square wave pulses of 0.2 msec duration at 1.0 Hz were delivered to the ulnar nerve at the wrist in Group I and simultaneously at 1.0 Hz and 0.15 Hz to both ulnar nerves in Group II. After establishing a stable control response, each subject received four or five doses of 0.1, 0.2, 0.3, 0.4 and 0.6 mg/kg. At least 10 minutes was allowed after complete recovery of the evoked twitch to control before each subsequent dose of BW785U was administered. Heart rate, blood pressure (intra arterial in Group II) and EKG were measured. Three dose response curves from the mean data points were constructed on log probit paper. Best fit straight lines were determined by probit regression by computer and goodness of fit of the data to straight lines was evaluated by Chi^2 test. Parallelism and the 95% Confidence limits were measured by the method of Litchfield and Wilcoxon.

Results. The results are summarized in Fig 1 and Table 1. Goodness of fit of the data to straight lines was highly significant by Chi^2 ($p<0.01$). The curves did not deviate significantly from parallelism ($p<0.05$). The potency of BW 785U in both awake and anesthetized subjects stimulated at 1.0 Hz is significantly greater than the potency at 0.15 Hz in anesthetized volunteers $p<0.05$ (Fig 1).

TABLE 1

ED50 and ED95 and their 95% Confidence limits

	Awake 1.0 Hz	Anesth 1.0 Hz	Anesth 1.0 Hz
ED_{50}	0.25 (0.13-0.47)	0.16 (0.08-0.3)	0.5 (0.25-0.97)
ED_{95}	0.52 (0.28-0.96)	0.33 (0.2-0.52)	1.05 (0.6-1.7)

(Anesth = Anesthetized)

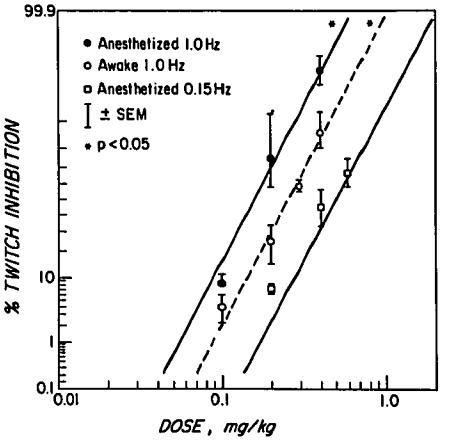

FIGURE 1

The ED50 and ED95 and their confidence limits are shown in Table 1. The apparent potency of BW785U in anesthetized volunteers stimulated at 1.0 Hz was 3.2 times greater than that at 0.15 Hz. This ratio is very similar to results obtained for d-tubocurarine (Anesthesiology 52:36-39, 1980) under the same conditions. The potency in awake volunteers at 1.0 Hz was twice that at 0.15 Hz in anesthetized volunteers.

Discussion and Conclusion. Since the dose-response curves generated in this study are parallel, it appears that the potency of BW 785U in anesthetized subjects was predictable from low dose studies in awake volunteers in whom the ulnar nerve was stimulated at 1.0 Hz. The latter frequency allows detection of the pattern and duration of the neuromuscular block produced by a nondepolarizing blocking agent at low systemic doses which do not produce severe generalized symptoms. In this study, the predicted clinically applicable ED95 at 0.15 Hz in anesthetized subjects was twice that calculated from awake unmedicated volunteers stimulated at 1.0 Hz.

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