Title: CLINICAL PHARMACOLOGY OF ATRACURIUM (BW33A) IN PEDIATRIC PATIENTS

Authors: D. Ryan Cook, M.D., G. David Rudd, M.S., and Barbara W. Brandom, M.D.

Affiliation: Department of Anesthesiology, University of Pittsburgh, Pittsburgh PA, and Department of Clinical Research, Burroughs Wellcome Co., Research Triangle Park, NC

INTRODUCTION

BW33A is a non-depolarizing neuromuscular blocking agent of short to intermediate duration. In adults it has been shown to be noncumulative and devoid of cardiovascular effects (1,2) at clinically useful doses. We (1) determined the dose-response relationships (ED95 and ED50) for BW33A following single dose administration and cumulative dose administration (3) and (2) the neuromuscular blocking effects and non-neuromuscular effects of BW33A at 400 ug/Kg.

METHODS: Twenty-four healthy boys, (median age = 13 yrs.) were studied during nitrous oxide-oxygen-halothane anesthesia. This study was approved by the Institutional Review Board and informed consent was obtained from a parent. End-tidal halothane averaged 0.8% at the time of BW33A administration. Immediately following BW33A administration heart rate and blood pressure were recorded at 1 minute intervals with a microprocessor (Dinamap). The ulnar nerve was supramaximally stimulated with repetitive trains-of-four (2 Hz for 2 seconds at 10 second intervals). The evoked compound electromyogram (EMG) of thumb adduction was recorded. Neuromuscular blockade was expressed as a percent of control of the first EMG height of the train-of-four.

Three groups of 5 boys received an initial bolus of either 80, 100, or 120 μg/Kg of BW33A. In 12 of these 15 patients an additional 1-2 doses of BW33A were given after the neuromuscular block had stabilized. Estimates of the ED95 and ED50 of BW33A were obtained by simple regression of the probit of the neuromuscular response and the logarithm of the dose in the single dose group and the cumulative dose group.

Another group of 9 patients recieved 400 μg/Kg BW33A to evaluate the safety and efficacy of a larger dose.

RESULTS: Neuromuscular blockade achieved from BW33A (mean ± SD) from 80 ug/Kg was 21.1 percent (± 11.2), from 100 ug/Kg was 42.2 percent (± 23.7), and from 120 ug/Kg was 76.8 percent (± 11.4). The estimated ED95 from the single dose regression line was 154 μg/Kg and the ED50 was 101 ug/Kg; the estimated ED95 from the cumulative dose regression line was 239 ug/Kg and the ED50 was 92 ug/Kg (Fig. 1).

At 400 μg/Kg (2.6 x ED95) BW33A produced 99.7 percent blockade (± 0.9) in 3 minutes (± 1.1). The time to recover to twenty-five percent neuromuscular transmission (T25) averaged 26.6 minutes (± 6.6); the time to seventy-five percent neuromuscular transmission was 36.3 minutes (± 6.7); the T25 - T75 interval was 9.0 minutes (± 1.4).

Following 400 ug/Kg BW33A the MAP changed by -0.4 mmHg (± 13.0) and the pulse by + 8.0 beats/min (± 8.9). No arrhythmias or signs of histamine release were noted. Intubating conditions were excellent in 7/9 patients.

DISCUSSION

The ED95 (single dose) of BW33A during halothane anesthesia in teenage boys is close to that reported in adults during nitrous oxide-narcotic anesthesia. This suggests that older children are somewhat "resistant" to BW33A as compared to adults. The cumulative dose response method over-estimates the ED95 of BW33A by 55 percent as compared to the single dose method. This is not surprising since BW33A is rapidly destroyed by spontaneous chemical decomposition (Hoffman elimination) and by ester hydrolysis.

Given the lack of cardiovascular effects and the relatively rapid recovery time, BW33A is a promising nondepolarizing relaxant of intermediate duration for pediatric patients.

REFERENCES

(1) Hughes R, Chappel DJ. The pharmacology of atracurium: A new competitive neuromuscular blocking agent. Br J Anaesth 1981; 53:31.

(2) Payne JP, Hughes R. Evaluation of atracurium in anesthetized man. Br J Anaesth 1981; 53:45.

(3) Donlon JV, Ali HH, Savarese JJ: A new approach to the study of four non-depolarizing relaxants in man. Anesth Analg 1974; 53:924-939.

Legend for Figure:
9.11 log x -13.2; r = 0.81. Line 2: y = 4.90 log x -5.0; r - .87)