Title: Comparative Pharmacology of BW B1090U in the Rhesus Monkey

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Introduction: In 1979[1] we described the preclinical pharmacology in the rhesus monkey of BW 785U, a short-acting, nondepolarizing ester neuromuscular blocking agent. During a brief clinical trial, the neuromuscular blocking activity of BW 785U was indeed very short. A hypotensive property had been noted in animals at the ED95 and higher doses. This effect, apparently due to histamine release, was much more prominent in humans, however, and forced the cancellation of further trials.[2] Additional structure-activity studies have since led to the development of BW B 1090U, a more potent ester material also showing a brief nondepolarizing blocking action. In this report we summarize the neuromuscular and cardiovascular effects of BWB1090U in the rhesus monkey, a species which we consider a good indicator of the actions of such substances in humans.

Methods: Adult rhesus monkeys (n=6) of either sex weighing 8-13 kg were anesthetized with thiopental 30 mg/kg and diazepam 1 mg/kg I.M. The trachea was intubated without a relaxant and anesthesia was maintained with halothane (0.5-1.0%) in $N_2O/O_2$ (70:30 mixture). Arterial pressure, heart rate and the twitch of the tibialis anterior, indirectly elicited at 0.15 Hz, were continuously recorded. Ventilation was controlled to maintain normal arterial gas values. Dose-response curves for neuromuscular blockade and cardiovascular effect were constructed. Appropriate statistical comparisons were made by t-test, analysis of variance, or linear regression on probit values.

In five separate experiments, the neuromuscular and cardiovascular effects of a very large dose of BWB1090U (0.2 mg/kg, or 5xED95) were noted when BWB 1090U was given as a first-bolus to virgin preparations. Ninety-five percent block was then re-established and maintained by continuous infusion for two hours. Recovery times from bolus doses and infusion were compared.

Hydrolysis rate in vitro by human plasma cholinesterase was determined.

Results: The hydrolysis rate was approximately 90% of that of succinylcholine.

The ED95 was 0.04 mg/kg. The duration of action at ED95 was 9-12 min, at 2.5xED95 12-15 min, and at 5xED95 14-20 min. Recovery rates are summarized in Table 1. The block showed fade of tetanus and train-of-four and was antagonized by anticholinesterases.

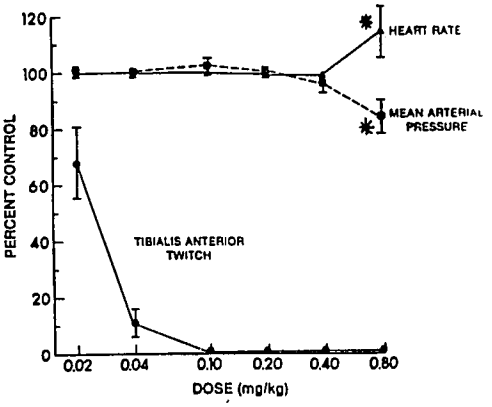
Table 1
Onset and Recovery Rates from BWB1090U*

| Dose (mg/kg) | ED95 Multiple and % Block | Onset (min) | Recovery Time (min) 25-75% | 5-95% |
|---|---|---|---|---|
| 0.04 | 95 | 1.7 | 3.4 | 8.5 |
| 0.10 | 100 | 1.4 | 3.5 | 8.6 |
| 0.20 | 100 | 1.0 | 4.1 | 9.1 |
| 2-hr infusion at 95% Block | | | 3.2 | 9.1 |

*SE's omitted for space

Cardiovascular changes became significant at 0.80 mg/kg (20xED95) (Fig 1). Cardiovascular effects after 5xED95 (0.2 mg/kg) when given either as the fourth dose in a series or as the first dose to a virgin preparation were not different and did not differ significantly from control values. Changes at 0.8 mg/kg were accompanied by facial erythema, showed tachyphylaxis, and were inhibited by $H_1$ and $H_2$ blockers.

Figure 1




Discussion and Conclusion: Like BW 785U, BW B 1090U is a short-acting nondepolarizing agent. Its safety margin is ten times as great as that of BW 785U. The duration of action is about one-third to one-half that of atracurium and vecuronium in the monkey.[3-4] BWB1090U seems worthy of clinical trial.

References:
1. Savarese JJ, Wastila WB: Anesthesiology 51:S277, 1979.
2. Rosow CE et al: Anesthesiology 53:S270, 1980.
3. Marshall IG et al: Br J Anaesth. 52:11S, 1980.
4. Hughes R, Chapple DJ: Br J Anaesth 53:31, 1981.