

Date :  
 Title : BW 785U: CORRELATION OF CARDIOVASCULAR EFFECTS WITH INCREASES IN PLASMA HISTAMINE  
 Authors : C.E. Rosow, M.D., Ph.D., S.J. Basta, M.D., J.J. Savarese, M.D., H.H. Ali, M.D.,  
 K.J. Kniffen, M.S., and J. Moss, M.D., Ph.D.  
 Affiliation: From the Anesthesia Services of the Massachusetts General Hospital and the Department  
 of Anaesthesia, Harvard Medical School, Boston, Massachusetts 02114.

### Introduction

BW 785U is a new bis-quaternary neuromuscular blocking agent which is currently undergoing Phase I clinical trials. It is a non-depolarizing relaxant with a rapid onset and short duration of action due to its rapid hydrolysis by plasma cholinesterase. Preliminary animal studies suggested that BW 785U had no significant cardiovascular effects at doses that produced partial or complete neuromuscular blockade in cats, dogs, monkeys and baboons. Supramaximal doses (2 to 8 times ED95) given to rhesus monkeys produced dose-related hypotension and tachycardia; these effects could be antagonized by pretreatment with a combination of H<sub>1</sub> and H<sub>2</sub> histamine receptor blockers. For this reason, our initial human protocols incorporated measurements of drug-induced histamine release. We utilized a newly developed radioenzymatic assay to compare histamine release by BW 785U, d-tubocurarine, and BW 785U in combination with antihistamines.

### Methods

Subjects were healthy volunteers, ages 18 to 39, who gave institutionally approved informed consent to participate in this trial. Fasted subjects were brought to the operating room where intravenous and intra-arterial cannulae were placed. General anesthesia was induced with thiopental (4-6 mg/kg) and maintained with N<sub>2</sub>O-O<sub>2</sub> and incremental doses of thiopental and fentanyl. Arterial pressure, pulse, EKG, temperature, arterial blood gases and thumb twitch were monitored. Venous blood was drawn for histamine determination 2 minutes before drug and at 2 and 5 minutes following each dose.

Each subject in Group I (N=4) received 0.2, 0.4, and 0.6 mg/kg BW 785U as separate bolus injections. The lowest doses were given first; after spontaneous recovery of 100% twitch, at least 10 minutes was allowed before administration of the next dose. Each volunteer in Group II (N=5) received intravenous diphenhydramine (1.0 mg/kg) and cimetidine (4.5 mg/kg) one hour before administration of BW 785U. Three doses (0.2, 0.6, and 1.2 mg/kg) were given in succession to each subject. Subjects in Group III (N=8) were studied under a separate but similar protocol and are included here for purposes of comparison. Each subject was given 0.5 mg/kg d-tubocurarine, and only one dose was administered per patient.

Plasma samples were assayed for histamine by a modification of the single isotope radioenzymatic assay described by Shaff and Beaven.<sup>1</sup> This method incorporates an additional chromatographic separation of the tritiated histamine derivative and has a sensitivity of 100 pg/ml (normal values are 600 to 1000 pg/ml). Dose-response relationships were measured by linear regression and analysis of variance.

### Results

Maximal changes in cardiovascular parameters and plasma histamine occurred within 2 minutes and had a duration of less than 5 minutes. Only the data for baseline and 2 minutes post-drug administration are presented in Table 1.

Group	Dose	$\Delta$ BP (torr)	$\Delta$ HR	Histamine (% Control)	Twitch (% Control)
I*	0.2	- 3	+ 3	108	6
	0.4	-18	+11	215	54
	0.6	-38	+24	260	85
II*	0.2	- 2	- 1	132	14
	0.6	-15	+ 5	1640	85
	1.2	-29	+10	6463	100
III	0.5	-12	+ 7	406	92

\*Dose-response for BP, HR and histamine significant (p<0.05). Slopes for Groups I and II significantly different for plasma histamine (p<0.01).

### Discussion

There is a great deal of individual variability in the release of histamine by a given dose of muscle relaxant, but both BW 785U and d-tubocurarine produced dose-related increases in plasma histamine. Decreases in BP and increases in HR occur at submaximal blocking doses with both drugs. In subjects not given antihistamine pretreatment (Group I), these changes correlate well with the increase in plasma histamine. By comparison, pretreatment with antihistamines results in a much larger increase in plasma histamine levels following BW 785U. This effect is presumably due to the known capacity of antihistamines to inhibit histamine N-methyl transferase, the principal route of histamine metabolism. Despite high histamine levels in this group, the cardiovascular effects were significantly less than in non-pretreated subjects.

BW 785U was given repeatedly to each subject, and we occasionally saw tachyphylaxis, which may have been due to histamine depletion. This was not a problem with Group III, since d-tubocurarine was only given once per subject. Although we may have underestimated the effect of high doses of BW 785U, the data suggest that it is at least equipotent with d-tubocurarine as a histamine releaser and slightly less potent as a muscle relaxant in man.

### Reference

- Shaff RE, Beaven MA. Anal Biochem 94: 425-430, 1979.