

Title: HISTAMINE-RELEASING POTENCIES OF ATRACURIUM BESYLATE (BW 33A), METOCURINE, AND *d*-TUBOCURARINE

Authors: S.J. Basta, M.D.; J.J. Savarese, M.D.; H.H. Ali, M.D.; J. Moss, M.D.; and M. Gionfriddo, B.A.

Affiliation: From the Anesthesia Services of the Massachusetts General Hospital and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts 02114.

## INTRODUCTION

A major reason for developing new neuromuscular blocking agents is that all currently used drugs have well known cardiovascular effects, some of which may be related to release of histamine, such as with *d*-tubocurarine.<sup>1</sup> Metocurine is a relaxant felt to be a weak histamine liberator.<sup>2</sup> Atracurium besylate (BW 33A) is a new nondepolarizing muscle relaxant of intermediate duration which has been shown to have little cardiovascular effect.<sup>3,4</sup> The purpose of this study was to 1) compare the relative abilities of atracurium and metocurine to release histamine; 2) correlate any resultant cardiovascular effect with serum histamine levels; and 3) establish neuromuscular blocking *vs* histamine-releasing dose-ratios for the two drugs and to compare these with data already generated for *d*-tubocurarine.

## METHODS

Elective ASA I-II surgical patients age 18-58 gave institutionally approved informed consent. Forty patients received atracurium; 24 received metocurine. All patients were premedicated with diazepam 0.1 mg/kg PO and morphine 0.15 mg/kg IM. Anesthesia was induced with fentanyl 4-8 µg/kg and thiopental 5-10 mg/kg IV and maintained using N<sub>2</sub>O:O<sub>2</sub> (4:2 L). Endotracheal intubation was accomplished with either atracurium or metocurine after all measurements had been made. Heart rate (HR, by tachygraph) and EKG were recorded continuously. Blood pressure (BP) was monitored in the atracurium group via indwelling radial artery catheters and in the metocurine group using an automated oscillometer ("Sentry," Bard Bio-medical). Neuromuscular blockade was monitored using evoked train-of-four responses (2 Hz for 2 secs repeated every 10 secs) of the ulnar nerve-adductor pollicis muscle system. After a stable baseline period of 15 mins, a single rapid (5 sec) bolus of either atracurium or metocurine was given. Maximum changes in HR and arterial pressure were recorded. Immediately before, and at 2 and 5 mins after drug injection, plasma histamine samples were drawn. Plasma samples were analyzed for histamine by an isotope radioenzymatic assay technique described previously.<sup>1</sup> The sensitivity of the assay is 100 pg/ml, the normal range being 600-1,000 pg/ml. Values were considered statistically significant when  $p < 0.05$ .

## RESULTS

Table 1 depicts those doses of metocurine and atracurium for which mean arterial pressure (MAP), HR and plasma histamine values first showed statistically significant changes from control values (all  $p < 0.05$ ). All data are expressed as means with standard error omitted due to space limitations. Data for *d*-tubocurarine<sup>1</sup> are included for comparison. MAP, HR and plasma histamine values at all dosage levels below those listed did not differ statistically from control. Maximum HR and arterial pressure changes

occurred 1 to 2 minutes post-drug injection and returned to normal within approximately 5 minutes.

## DISCUSSION

Studies of *d*-tubocurarine and the experimental neuromuscular blocking agents BW 785U<sup>5</sup> and BWA 444U<sup>6</sup> have shown both dose-dependent release of histamine and correlation of plasma histamine levels with HR and BP changes. In this and the above studies, it appears that a dose of relaxant which increases plasma histamine to about 200% of control levels will result in clinically and statistically significant arterial pressure and HR changes. It should also be noted that as the dose of relaxant is increased, the proportion of patients exhibiting a two-fold rise in plasma histamine also increases and contributes most to the mean data calculated. From the present study it appears that atracurium's ability to release histamine, relative to its neuromuscular blocking potency, is approximately one-half that of metocurine and less than one-third that of *d*-tubocurarine.

Table 1

Drug	Dose (mg/kg)	n	ED <sub>95</sub> Multiple	Percent of Control		
				MAP	HR	Histamine
<i>d</i> TC <sup>1</sup>	0.50	6	1	77.9	116.4	410
mTC	0.50	8	2	79.1	118.9	211.8
BW 33A	0.60	10	3	79.5	108.3	192.1

*d*TC = *d*-tubocurarine; mTC = metocurine; BW 33A = atracurium

## References

1. Moss J, Rosow CE, Savarese JJ, *et al*. Anesthesiology 55: 19-25, 1981.
2. Savarese JJ, Ali HH, Antonio RP. Anesthesiology 47: 227-284, 1977.
3. Payne JP, Hughes R. Br J Anaesth 53: 45-54, 1982.
4. Basta SJ, Sunder N, Savarese JJ, *et al*. Anesth Analg 61: 169-170, 1982.
5. Rosow CE, Basta SJ, Savarese JJ, *et al*. Anesthesiology 53(3S): S-270, 1980.
6. Basta SJ, Moss J, Savarese JJ, *et al*. Anesthesiology 55(3A): A-198, 1981.