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# The Clinical Pharmacology of BW A444U

## A Nondepolarizing Ester Relaxant of Intermediate Duration

John J. Savarese, M.D.,* Hassan H. Ali, M.D.,* Salvatore J. Basta, M.D.,† Neelakantan Sunder, M.D.,†
Jonathan Moss, M.D., Ph.D.,‡ Michael A. Gionfriddo, B.A.,§ Charles G. Lineberry, Ph.D.,¶
William B. Wastila, Ph.D.,** Hassan A. El-Sayad, Ph.D.,†† Debbie Montague, R.Ph.‡‡
Leon Braswell, B.S.§§

**The clinical pharmacology of BW A444U, a nondepolarizing ester relaxant, was evaluated in 56 consenting ASA class I subjects under nitrous oxide/oxygen–fentanyl–thiopental anesthesia. Using repetitive train-of-four stimulation, the $ED_{95}$ for inhibition of the first twitch in the train ($T_1$) was 0.11 mg/kg. At 0.12 mg/kg, 97% inhibition of $T_1$ developed within 4.6 ± 0.6 (SE) min from injection; recovery of $T_1$ to 95% of the control height occurred within 52.3 ± 3.1 min. In a comparative group of subjects given 0.5 mg/kg *d*-tubocurarine, onset and depth of block were not significantly different, but the duration of recovery of $T_1$ to 75% of control was at least three times longer ($P < 0.001$). The duration of BW A444U-induced block therefore may be classified as intermediate between *d*-tubocurarine and succinylcholine. There was little cumulative effect, since 5 → 25 and 25 → 75% recovery times did not vary significantly on either repetitive or increasing dosage. These properties may be explained at least in part by the finding that BW A444U is hydrolyzed relatively slowly *in vitro* by human plasma cholinesterase, at 5.4% the rate of succinylcholine. Consistent with these observations, at the $ED_{100}$ (0.2 mg/kg) there was a significant inverse linear correlation between the duration of block and plasma cholinesterase activity. Neuromuscular block by BW A444U was antagonized readily by neostigmine.**

**No changes in arterial pressure or heart rate were noted at up to 0.12 mg/kg (97% block). At higher dosages (0.16–0.20 mg/kg), brief (2 to 5 min), moderate decreases in mean arterial pressure, slight increases in heart rate, and facial erythema were observed occasionally. These changes correlated well with small increases in serum histamine.**

**The human neuromuscular pharmacology of BW A444U suggests that nondepolarizing relaxants of intermediate duration of action may be produced from ester materials slowly hydrolyzed by plasma cholinesterase, and that BW A444U may have certain clinical pharmacologic advantages over current nondepolarizing relaxants. (Key words: Histamine: release. Antagonists, neuromuscular relaxants. Neuromuscular relaxants: BW A444U; cardiovascular effects.)**

WE HAVE ADVOCATED the synthesis of quaternary ester compounds rapidly hydrolyzed by human plasma cholinesterase as a means of producing short-acting nondepolarizing relaxants.[1,2] Such materials, if broken down relatively slowly by plasma cholinesterase, might serve as nondepolarizing neuromuscular-blocking drugs of intermediate duration (40–60 min) in humans.[3] There is a clinical need for such substances.[3] In fact, two new materials, ORG NC45 (vecuronium), a steroidal analogue of pancuronium, and BW 33A (atracurium), a bis-benzylisoquinolinium diester, do show such intermediate duration and have already undergone rather extensive clinical trials.[4–8]

We have recently reported that in experimental studies in animals, a new nondepolarizing ester material, BW A444U (fig. 1), did show intermediate duration, as well as a lack of cardiovascular effect.[9] These properties seemed clinically desirable and the compound has been subjected to human trials. Some of the results have been presented briefly in abstract form.[10,11] This report details the clinical pharmacology of BW A444U. The purposes of the study were to determine the new compound's neuromuscular-blocking potency, duration of action, antagonism by neostigmine, and cardiovascular effect in anesthetized human subjects, to correlate the duration of neuromuscular effect with the individual subject's plasma cholinesterase activity, and to ascertain whether any cardiovascular effect might reflect changes in serum histamine levels, since this mechanism may have been responsible for a slight hypotensive effect noted at very high dosage in animals.[9]

* Associate Professor of Anaesthesia, Harvard Medical School; Associate Anaesthetist, Massachusetts General Hospital.

† Instructor in Anaesthesia, Harvard Medical School; Assistant Anaesthetist, Massachusetts General Hospital.

‡ Assistant Professor of Anaesthesia, Harvard Medical School; Assistant Anaesthetist, Massachusetts General Hospital. Present address: Massachusetts Eye and Ear Infirmary, Boston.

§ Clinical Research Coordinator, Department of Anaesthesia, Massachusetts General Hospital.

¶ Senior Clinical Research Scientist and Project Leader, Medical Division, Wellcome Research Laboratories, Burroughs Wellcome Company.

** Group Leader, Department of Pharmacology, Wellcome Research Laboratories, Burroughs Wellcome Company.

†† Senior Developmental Chemist, Chemical Development Laboratories, Burroughs Wellcome Company.

‡‡ Pharmacy Fellow, Medical Division, Wellcome Research Laboratories, Burroughs Wellcome Company.

§§ Technical Assistant.

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Address reprint requests to Dr. Savarese: Department of Anaesthesia, Massachusetts General Hospital, Fruit Street, Boston, Massachusetts 02114.

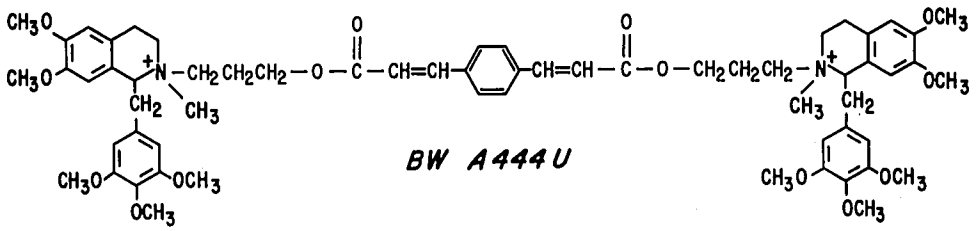


FIG. 1. Structural formula of BW A444U, a bis-benzylisoquinolinium diester of p-phenylene diacrylic acid.

## Methods

### PATIENT AND VOLUNTEER STUDIES

The study was approved by the Human Studies Committee of Massachusetts General Hospital. A brief initial trial was conducted in eight healthy volunteers. Forty-eight ASA Class I patients undergoing elective peripheral surgical procedures were then studied. All subjects gave written informed consent. Since both volunteer and patient studies were conducted in identical fashion, the results are combined in this report. The mean ages and weights of all individuals (±SE) were 28.6 ± 1.0 years and 76.8 ± 1.4 kg, respectively.

All subjects received diazepam (0.1–0.2 mg/kg) orally and/or morphine (0.1–0.15 mg/kg) im one hour before induction of anesthesia. A large-bore venous cannula and 20-gauge radial arterial cannula were placed percutaneously while the subjects were under local anesthesia. Anesthesia was then induced with thiopental (6–8 mg/kg) iv and fentanyl (5–10 μg/kg) iv in divided doses and with nitrous oxide and oxygen in a semiclosed system (66/33% inspired concentration). Anesthesia was maintained with the same gas concentration and with additional thiopental and/or fentanyl, as necessary. The trachea was sprayed with 4% lidocaine and intubation was performed without a relaxant. Alternatively, the trachea was intubated under BW A444U-induced neuromuscular blockade after the maximal neuromuscular and cardiovascular effects of the drug had been ascertained. Ventilation was controlled manually via a face mask or mechanically via the endotracheal tube to maintain arterial gas values within normal limits ($Pa_{CO_2}$ 35–45 mmHg). Esophageal temperature was maintained between 35 and 37.5° C. Force of thumb adduction was quantitated with a Grass® FT-10 transducer by a method previously described.[12] Repetitive train-of-four stimulation (2 Hz for 2 s repeated every 10 s[13]) was applied to the ulnar nerve at the wrist through 22-gauge steel needle electrodes placed subcutaneously. Square wave pulses at supramaximal voltage were generated by a Grass S 88 stimulator via an isolation unit. Repetitive train-of-four stimulation was used not only to quantitate the depth of block, but also to confirm the nondepolarizing character of BW A444U-induced block.

Direct arterial pressure was recorded using Statham®, Bell and Howell®, or Tektronix® transducers. The electrocardiogram was monitored continuously on an oscilloscope (Tektronix model 412) capable of generating a printout in case of an abnormality. Heart rate was recorded continuously with a Grass 7P44 tachograph triggered by either the R-wave of the electrocardiogram or by the arterial pulse wave. All measurements were transcribed simultaneously on a Grass model 7 polygraph.

After at least a 15-min stable baseline period, BW A444U was injected as a moderately rapid (15–30 s) bolus into a smoothly flowing iv stream. Measurements of maximal twitch, arterial pressure, and heart rate changes were obtained before any patient stimulation (laryngoscopy or surgery) was initiated. Surgery was then begun. Full recovery to a value of at least 95% of control of the first twitch ($T_1$) in the train-of-four response and to a train-of-four ratio of 80% or more was allowed after the initial dose of BW A444U. Then, if further surgical relaxation was needed, at least 95% inhibition of $T_1$ was again induced with a second appropriate dose of BW A444U. When $T_1$ had recovered to 25% of the control height after this second dose of BW A444U, a third dose, standardized at 0.04 mg/kg, was given. Subsequent dosage also was standardized at 0.04 mg/kg and was given each time $T_1$ reached 25% of control. In this manner the cumulative property of BW A444U, if any, was tested by noting whether the interval between repeated 0.04 mg/kg doses lengthened or whether the successive recovery time of $T_1$ from 5 to 25% of the control value became longer.

The dose-response curve for BW A444U-induced block was constructed by computerized regression of probit values obtained from the percentage block of $T_1$ achieved. The method is essentially that of Litchfield and Wilcoxon.[14]

To compare the duration of neuromuscular blocking effect of BW A444U with that of the standard agent *d*-tubocurarine, control studies were done (n = 16) at the $ED_{95}$ (0.5 mg/kg). The conditions were identical for subjects studied with BW A444U.

### ANTAGONISM OF NEUROMUSCULAR BLOCKADE

When indicated, antagonism of residual BW A444U-induced block was tested by administering a mixture of

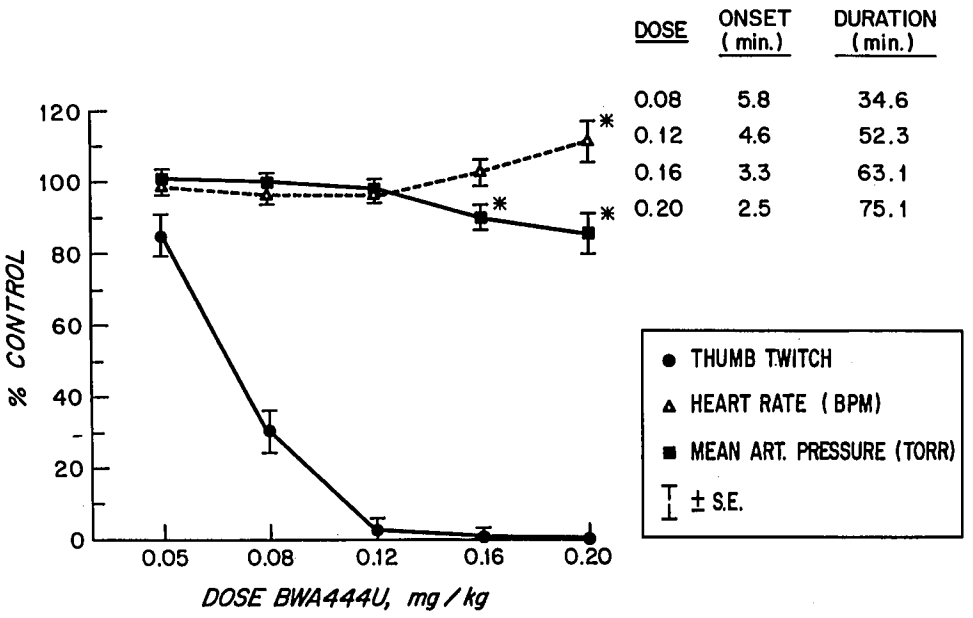


FIG. 2. Summarized maximal neuromuscular and cardiovascular effects of BW A444U in subjects under nitrous-oxide–fentanyl–thiopental anesthesia. The tendency toward divergence of arterial pressure and heart rate from control values at higher dosages is characteristic of a weak histamine-releasing property (See Results and Discussion sections). Onset and duration represent times from injection to maximum neuromuscular block and to 95% twitch ($T_1$) recovery. Maximal changes in arterial pressure were significantly different from control values at 0.16 and 0.2 mg/kg. The change in heart rate was statistically significant only at 0.2 mg/kg. *Indicates $P < 0.05$.

neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg) as a 30- to 60-s intravenous bolus. The time from injection of the antagonist mixture to recovery of $T_1$ to 95% of the control height was measured.

### Dibucaine Number and Plasma Cholinesterase Activity

Arterial samples for this determination were drawn prior to induction of anesthesia. The method used was essentially that of Kalow and Genest.[15]

### Serum Histamine Determination

Arterial samples for this measurement were drawn immediately before administration of BW A444U, and two and five minutes after drug injection. Samples were drawn only at higher BW A444U dosages (0.12, 0.16, and 0.20 mg/kg). Histamine levels were assayed by a radioenzymatic technique recently described by Moss *et al.*[16] in a study of *d*-tubocurarine. The clinical procedure was identical in the two studies.

### Interaction with Cholinesterases

The rate of hydrolysis of BW A444U (relative to that of succinylcholine), as catalyzed by human plasma cholinesterase, was measured *in vitro* and calculated according to a method previously described.[17]

### Statistics

Appropriate comparisons were made by linear regression, Student's *t* test or F test analysis of variance.[18] Testing for parallelism of the dose-response curves of BW A444U and other nondepolarizing relaxants was done by the method of Litchfield and Wilcoxon.[14]

## Results

Neuromuscular and cardiovascular data are summarized in figure 2 and table 1. These results represent measurements made after only the first single bolus of BW A444U given to each of the 56 subjects studied.

### Neuromuscular-blocking Potency and Duration

The $ED_{95}$ was 0.11 mg/kg. BW A444U is therefore approximately half as potent as pancuronium, 2.5 times as potent as metocurine, and four times as potent as *d*-tubocurarine[19] (fig. 3). The dose-response curve did not differ significantly from parallelism with those of the standard agents ($P < 0.05$). The block was typically nondepolarizing, evidenced by increasing train-of-four fade as the block deepened.

At 0.12 mg/kg, a dose which produced 97% block, the duration of effect to 95% recovery of $T_1$ indicates that BW A444U-induced block lasts about one-third as long as that of *d*-tubocurarine block at similar depth (table 1). In fact, once recovery had begun, the dissipation of block by BW A444U was significantly faster ($P < 0.001$) than recovery from *d*-tubocurarine—about three to four times as rapid (note comparative 25 → 75% recovery times for $T_1$) (table 1).

Examination of 25 → 75% recovery times after various doses of BW A444U (table 1) suggests that the compound does not have an important cumulative prop-

TABLE 1. Neuromuscular-blocking Properties of BW A444U in Subjects under Nitrous Oxide Anesthesia

| Drug | Dose (mg/kg) | n | % Block ± SE | Onset* (min ± SE) | 75% Recovery* (min ± SE) | 95% Recovery* (min ± SE) | 25 → 75% Recovery (min ± SE) |
|---|---|---|---|---|---|---|---|
| BW A444U | 0.05 | 10 | 14.8 ± 6.1 | 4.5 ± 0.6 | —— | 16.6 ± 2.3 | —— |
| BW A444U | 0.08 | 12 | 69.3 ± 6.3 | 5.8 ± 0.4 | 27.2 ± 3.3 | 34.6 ± 3.4 | 14.1 ± 1.4 |
| BW A444U | 0.12 | 11 | 96.6 ± 1.4 | 4.6 ± 0.6 | 43.5 ± 3.3 | 52.3 ± 3.1 | 13.7 ± 0.7 |
| BW A444U | 0.16 | 12 | 99.0 ± 1.0 | 3.3 ± 0.4 | 55.4 ± 3.8 | 63.1 ± 3.6 | 14.7 ± 0.9 |
| BW A444U | 0.20 | 11 | 100 | 2.5 ± 0.2‡ | 66.4 ± 4.4 | 75.3 ± 5.0 | 16.9 ± 1.8 |
| *d*-tubocurarine | 0.50 | 16 | 98.4 ± 0.6 (NS) | 3.9 ± 0.9 (NS)† | 137 ± 9.0§ | —— | 52.2 ± 4.2¶ |

* Onset, 75% and 95% recovery times recorded from moment of completed injection.

(NS) Not significant ($P > 0.05$) *vs.* 0.16 mg/kg BW A444U.

† (NS) Not significant ($P > 0.05$) *vs.* 0.12, 0.16, or 0.20 mg/kg BW A444U.

‡ Significantly faster than at 0.12 or 0.16 mg/kg BW A444U ($P < 0.05$).

§ $P < 0.001$ *vs.* BW A444U recovery time to 75% twitch height at 0.16 mg/kg.

¶ $P < 0.001$ *vs.* BW A444U 25 → 75% recovery times at all doses.

erty, since these times did not differ significantly ($P > 0.05$). Further evidence supporting this conclusion was obtained by comparing 5 → 25% recovery times for $T_1$ after the initial and final doses of BW A444U in a group of seven patients who received at least four successive doses of the drug (see fig. 4). These times averaged 10.1 ± 0.7 and 10.9 ± 0.6 min, respectively. The difference is not significant ($P > 0.05$).

## Onset of Block

At BW A444U dosage producing 97–99% block (0.12–0.16 mg/kg), the onset of maximal effect, measured from the moment of injection, was not significantly different from the onset time (table 1) for a comparable dose of *d*-tubocurarine (0.5 mg/kg). Onset of block at 0.2 mg/kg BW A444U was significantly faster (2.5 ± 0.2 min) than at 0.12 or 0.16 mg/kg. The comparison *vs.* 0.5 mg/kg *d*-tubocurarine, however, did not reach statistical significance. The faster onset at 0.2 mg/kg was achieved at a cost of only 19% increase in duration of action *vs.* that at 0.16 mg/kg (75.3 *vs.* 63.1 min).

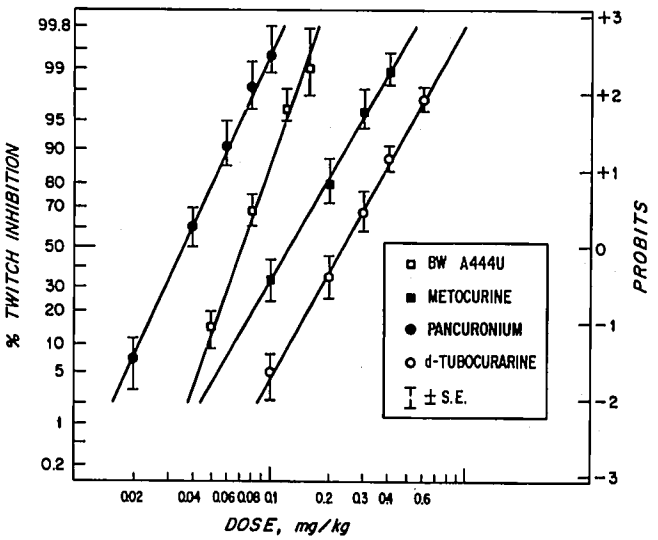


FIG. 3. The dose-response curve for neuromuscular blockade by BW A444U in subjects under nitrous-oxide–fentanyl–thiopental anesthesia, in comparison with curves for standard agents previously derived[19] under similar conditions. The curves do not differ significantly from parallelism.

## Hydrolysis and Relation to Pseudocholinesterase Activity

BW A444U is hydrolyzed *in vitro* by purified human plasma cholinesterase at 0.12 ± 0.28 mol/h, or approximately 5.4% the rate of succinylcholine (mean of three separate determinations). This relatively slow rate of hydrolysis, however, may provide sufficient explanation for the intermediate duration and relative lack of cumulative effect of the drug.

The duration of block at 0.2 mg/kg, a dose which produced 100% twitch inhibition in all subjects, was inversely related to the individual subject's plasma cholinesterase activity (fig. 5). The relation was statistically significant ($r = -0.73$, $P < 0.05$). This observation is supportive of the *in vitro* measurements.

No individual who received BW A444U during this clinical trial showed abnormally reduced plasma cholinesterase activity or atypically low dibucaine number.

## Antagonism by Neostigmine

Residual block by BW A444U was antagonized readily in 18 subjects by a mixture of neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg). The time to achieve 95% recovery of $T_1$ was inversely related to the depth of block at the time of antagonist administration (fig. 6). The latter data are typical of other nondepolarizing relaxants.[19,21] Although we have not attempted direct statistical comparisons, the speed of antagonism of BW A444U-induced block and the dosage of neostigmine required seem roughly comparable to data reported for metocurine, pancuronium, and *d*-tubocurarine.[19–21]

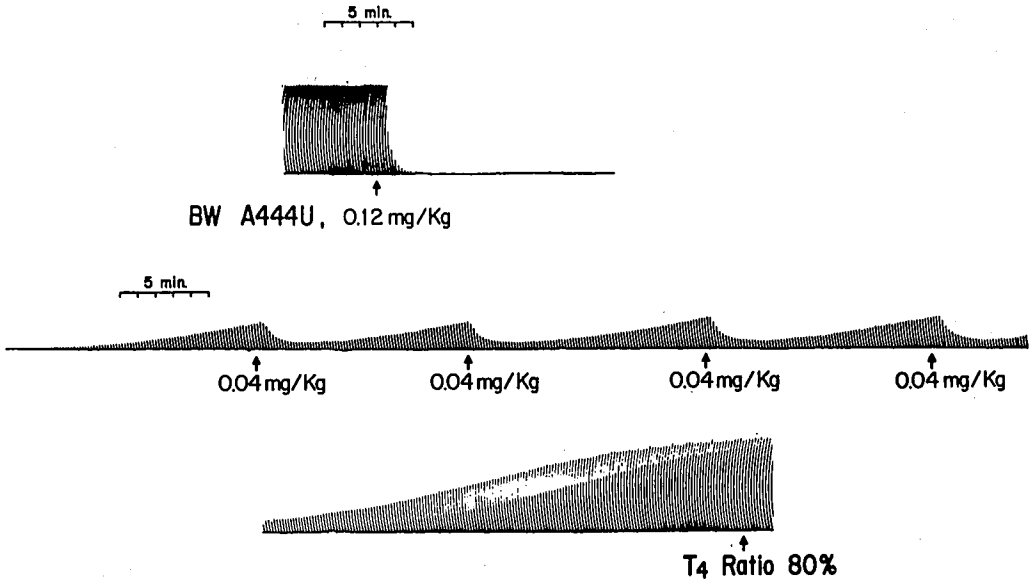


FIG. 4. Demonstration of the lack of cumulative effect of BW A444U in an individual subject. Continuous recording of repetitive train-of-four adductor responses of the thumb, indirectly elicited at 2 Hz for 2 s every 10 s. Note similar recovery pattern after each dose. The first, second, third, and fourth twitches of the train-of-four response are shown to recover *pari passu* after the last dose of BW A444U (see also tables 1 and 2). Time from last BW A444U dose (0.04 mg/kg) to train-of-four ($T_4$) value of 80% and recovery of $T_1$ to 95% of the control value: 30 minutes.

### CARDIOVASCULAR EFFECTS

No cardiac arrhythmias attributable to BW A444U were observed. At up to 0.12 mg/kg, a dose which caused 97% mean twitch inhibition, no significant changes in heart rate or mean arterial pressure were noted. At higher dosage (0.16–0.2 mg/kg), a tendency to produce a brief decrease in arterial pressure and a slight increase in heart rate was observed (fig. 2). In most individuals where such a cardiovascular response was seen, serum histamine levels increased (fig. 7) and a variable degree of skin erythema, particularly on the face and neck, could be detected for a period of 2–5 min after drug injection. The degree of hypotension and increase in heart rate were dose-related and directly related in both cases ($P < 0.001$) to increases in serum histamine levels (figs. 8*A* and 8*B*). Baseline histamine levels during these studies were within normal limits.[16] BW A444U, therefore, has a relatively weak histamine-releasing property which becomes evident at fully paralyzing dosage.

## Discussion

The clinical neuromuscular pharmacology of BW A444U generally substantiates preclinical estimates based on studies performed in several animal species. Consistent with observations made in rhesus monkeys, whose plasma cholinesterase activity in similar to that of humans,[22,23] BW A444U is a potent nondepolarizing relaxant of intermediate duration—approximately one-third that of *d*-tubocurarine[9]—and its neuromuscular-blocking effect is noncumulative. Its length of action and its lack of cumulative tendency fit already proposed criteria for an agent of this type[3]; it is reasonable to assume that these properties may be due, at least in part, to relatively slow hydrolysis of BW A444U by plasma cholinesterase. The high potency of BW A444U in humans is similar to its activity in rhesus monkeys and is unprecedented among nondepolarizing ester compounds of its general class. It is reasonable to generalize, based on the above clinical properties of BW A444U and on the clinical neuromuscular effects of an earlier material (BW Y100¶¶) that nondepolarizing compounds which are slowly hydrolyzed by human plasma cholinesterase (*i.e.*, at roughly 5 to 10% the rate of succinylcholine) should demonstrate an intermediate duration of effect in humans.

The ready antagonism of BW A444U-induced block by neostigmine in humans is a reassuring observation. We have previously expressed some concern that neuromuscular blockade produced by nondepolarizing relaxants which are hydrolyzed by plasma cholinesterase might not be subject to antagonism by acetylcholinesterase inhibitors[1,2] because the latter drugs also inhibit plasma cholinesterase.[24] Inactivation of the nonspecific plasma enzyme by neostigmine and other carbamates, however, is generally less prominent than inactivation of acetylcholinesterase.[24] Sunew and Hicks, in fact, have shown that significant (>75%) antagonism of human plasma cholinesterase *in vivo* by a large dose (5 mg) of neostigmine lasted less than 20 min.[25] It is possible to suggest, therefore, that during reversal by anticholines-

¶¶ Savarese JJ, Ali HH, Donlon JV, Antonio RP: The clinical effects of BW Y100 (compound AA-136) a new short-acting nondepolarizing neuromuscular blocking agent: correlation with experimental pharmacology. Abstracts of Scientific Papers, American Society of Anesthesiologists' annual meeting, Chicago, 1975, pp 193–194.

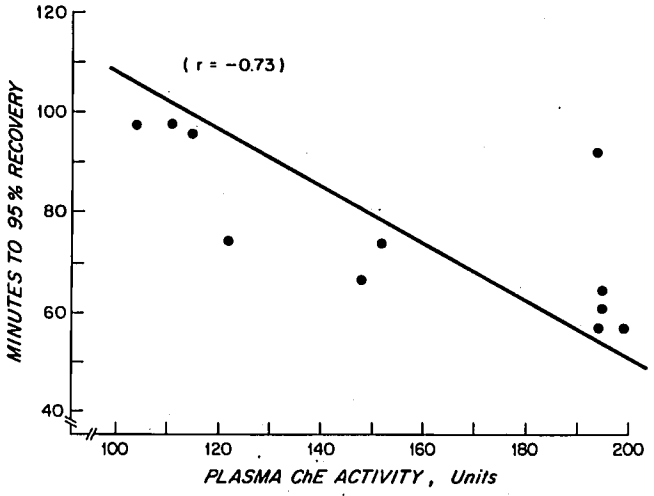


FIG. 5. A significant ($P < 0.05$) linear correlation was noted between the duration of BW A444U-induced block at 0.2 mg/kg (a dose which produced 100% twitch inhibition in all subjects) and the individuals' plasma cholinesterase activities. Abscissa: plasma cholinesterase activity (Kalow units[15]); ordinate: duration of block from injection to 95% recovery of $T_1$. This observation supports measurement *in vitro* of relatively slow plasma cholinesterase-catalyzed hydrolysis of BW A444U.

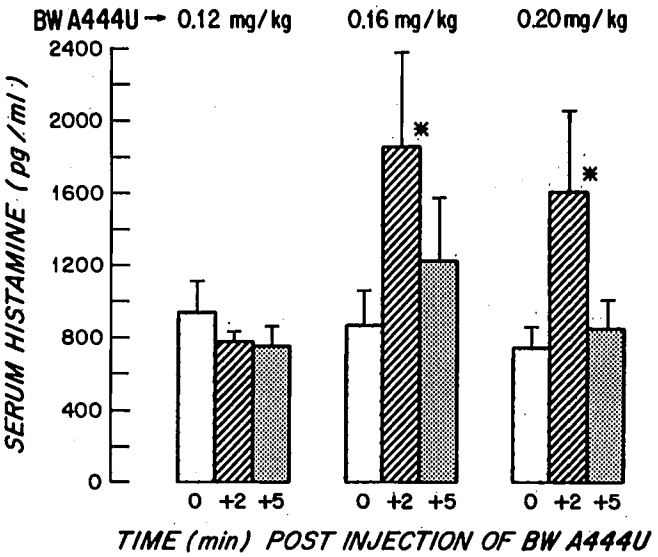


FIG. 7. Serum histamine changes after higher bolus doses of BW A444U. All values are means ± SE. Increases in serum histamine levels peaked at 2 min after drug injection and were statistically significant at both 0.16 and 0.20 mg/kg. *$P < 0.05$ *vs.* control level.

terases of nondepolarizing block produced by compounds such as BW A444U which are relatively poor substrates for plasma cholinesterase, the following dynamics may apply. During spontaneous recovery from block by BW A444U and related compounds, the speed of recovery probably is governed to a considerable degree by the rate of hydrolysis of the compound by plasma cholinesterase. When an anticholinesterase is administered during the recovery pattern, hydrolysis of the compound is likely to be slowed or stopped for a brief period, as in the case of succinylcholine,[25] due to inhibition of plasma cholinesterase. Antagonism of the block, however, is accomplished as in the case of other truly competitive standard nondepolarizers, because of acetylcholinesterase inactivation. Presumably, any residual ester material is then destroyed as the function of plasma cholinesterase begins to recover approximately 20 min later.[25] By this time, antagonism of the block should have been completed (see fig. 6).

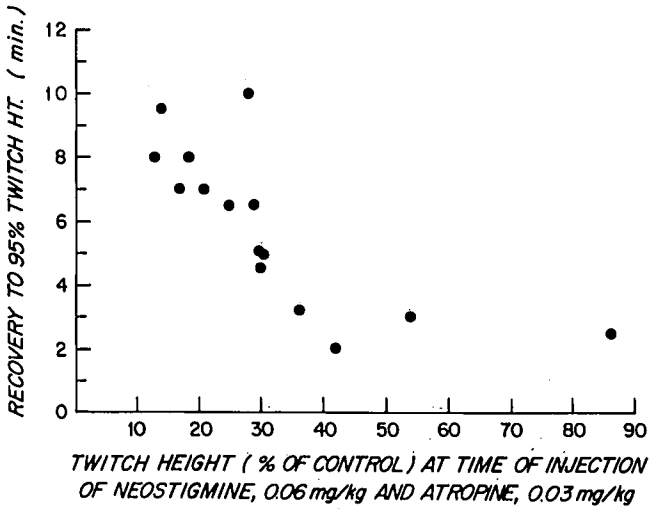


FIG. 6. Time course of antagonism of BW A444U neuromuscular blockade by neostigmine and atropine. Each point represents reversal of residual BW A444U-induced block in a single individual. As with other nondepolarizing relaxants,[19-21] speed of antagonism was inversely related to depth of block at the time of administration of the antagonist.

It is possible, although not tested in the present study, that edrophonium, which is now undergoing some clinical renaissance,[26-28] might prove a better antagonist of nondepolarizing ester compounds such as BW A444U than the carbamates. Edrophonium is a weaker anticholinesterase than neostigmine[25] and much of its antagonistic effect on nondepolarizing block may be due to facilitation of acetylcholine mobilization and release by the motor nerve terminal.[25,29] Consequently, inhibition of hydrolysis of nondepolarizing ester compounds by edrophonium might be less than that of the carbamates, resulting in more facile antagonism of the block.

A somewhat unpleasant surprise encountered during the present clinical trial of BW A444U was the documentation in humans of a relatively weak histamine-releasing property. This became apparent at the extreme upper end of the clinical dose range, *i.e.*, at 15-s bolus dosage of 0.16 mg/kg (the $ED_{99}$). The neuromuscular block *vs.* histamine release dose-ratio in humans for BW A444U is evidently smaller than it is in animals, since

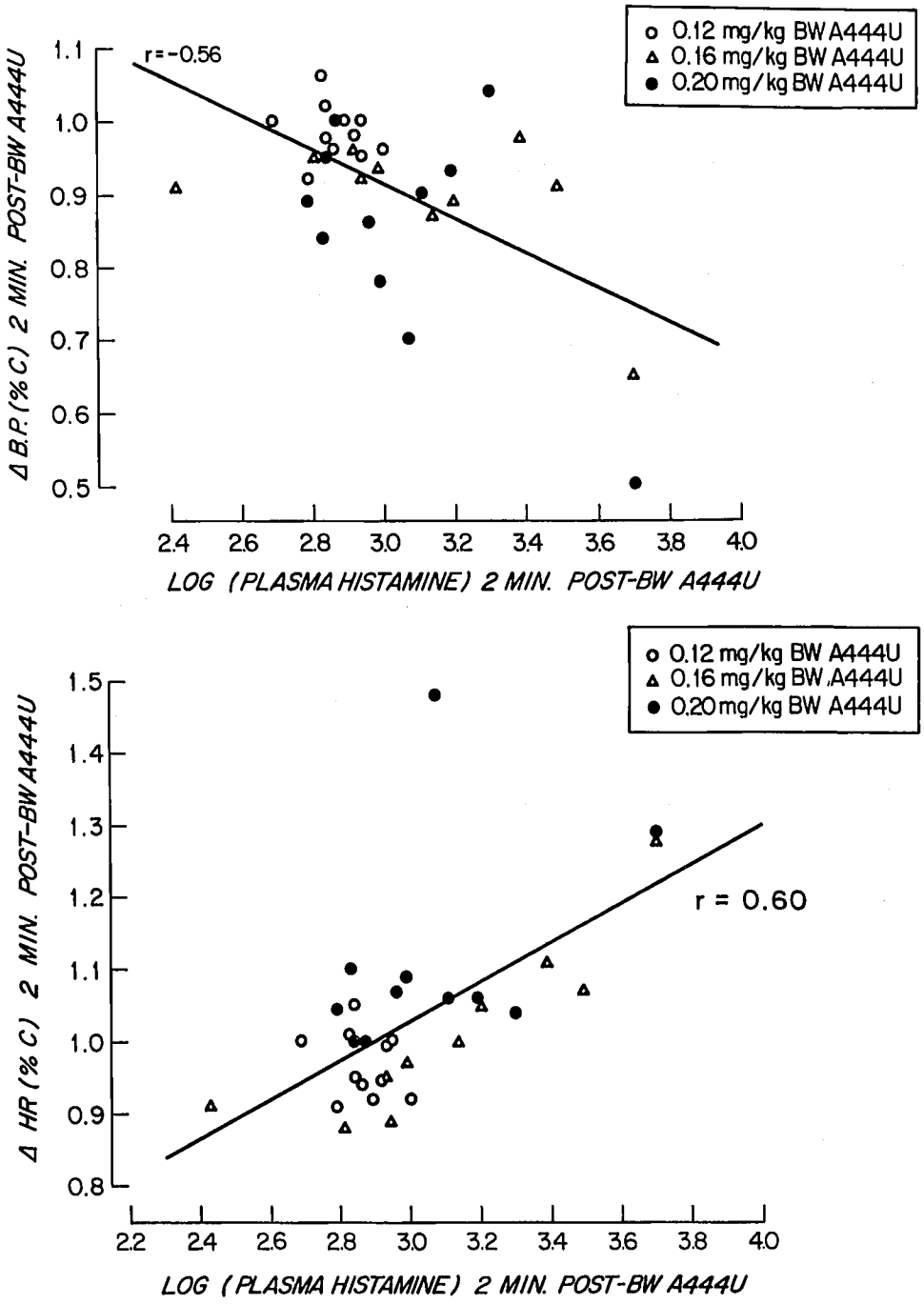


FIG. 8. Correlation of serum histamine levels 2 min after injection of BW A444U with decreases in mean arterial pressure (*A*, *top*) and increases in heart rate (*B*, *bottom*) at that time. The fall in mean arterial pressure and increase in heart rate were directly related to the dose of BW A444U and to the serum histamine concentration. The relationship was highly significant ($P < 0.001$ in both cases), indicating that the cardiovascular effect of BW A444U is probably due to a relatively weak histamine-releasing property (see text for further details).

cardiovascular changes suggestive of histamine release were not observed in animals until at least 2.5 times the $ED_{95}$ for neuromuscular blockade.[9] We would consider 0.16 mg/kg BW A444U as the upper end of the clinical dose range since we would most likely recommend this dose for tracheal intubation. Nondepolarizing relaxants usually produce good intubating conditions at the $ED_{99}$ dosage level (*e.g.*, pancuronium, 0.08–0.10 mg/kg; metocurine, 0.4 mg/kg; and *d*-tubocurarine, 0.6 mg/kg[19]).

Suspicion of mild histamine release by BW A444U initially was raised on clinical observation of facial erythema and a brief decrease in arterial pressure and increase in heart rate in some individuals receiving 0.16–0.20 mg/kg and was confirmed by excellent correlation of serum histamine levels with the cardiovascular changes (figs. 8*A* and 8*B*). The divergence of arterial pressure and heart rate from control levels as bolus dosage is increased (fig. 2) is quite characteristic of a relaxant whose cardiovascular effects are mainly due to release of histamine (see also Basta *et al.*,[8] Moss

*et al.*,[16] and Savarese *et al.*[19]) and might be considered good circumstantial evidence of its occurrence in the absence of actual serum histamine determinations.

BW A444U may be termed a relatively weak histamine-releaser since in the $ED_{95}$ range (0.12 mg/kg) there was no clinical evidence of histamine release and no change in serum histamine levels. At the $ED_{99}$ (0.16 mg/kg), only a twofold increase in serum histamine levels was measured. This may be compared with fourfold and six- to eightfold increases in histamine concentrations produced by *d*-tubocurarine at approximate $ED_{95}$ and $ED_{99}$ dosages (0.5 and 0.6–0.75 mg/kg, respectively).[16] In fact, in a study just completed by our group (data in preparation) it appears that the histamine-releasing potency of metocurine, relative to its neuromuscular-blocking activity, is very similar to that of BW A444U: at metocurine dosage in the $ED_{95}$ range (0.25 mg/kg) given as a 15-s bolus there is no significant change in serum histamine levels, whereas at $ED_{99}$ dosage of metocurine (0.4 mg/kg), given at the same rate, significant increases do occur. Certainly the neuromuscular *vs.* cardiovascular profiles of metocurine and BW A444U are very similar (compare fig. 2 with a similar figure for metocurine[19]).

On the basis of its shorter duration of action, lack of cumulative effect, easy reversibility, and relative lack of cardiovascular effect, BW A444U does offer advantages over currently available nondepolarizing relaxants and its clinical trial may be considered a success, *i.e.*, its safety and efficacy have been proven in humans. The same neuromuscular advantages, however, also have been amply demonstrated for two other new nondepolarizers: ORG NC45 (vecuronium) and BW 33A (atracurium), both of which have undergone more extensive clinical evaluation[4–8] than BW A444U. Both vecuronium[4–6] and atracurium[7,8] are probably slightly shorter in duration of action than BW A444U, although all three may be classified as relaxants of intermediate duration.[3] Both atracurium[7,8] and vecuronium[30] also show a wider separation of cardiovascular effect from neuromuscular blocking effect than BW A444U.

The clinical success within a short period of time (1979–1982) of three new nondepolarizing relaxants which are either actively metabolized, degraded, and/or relatively rapidly cleared, represents a transition from presently available nonmetabolized nondepolarizers which are mainly dependent upon relatively slow clearance by the kidney for their elimination. Many clinical implications should follow as a result of this transition.

Interestingly, both BW A444U and BW 33A (atracurium) have been produced more or less simultaneously by the same manufacturer. Clinical trials have indicated the pharmacologic superiority of atracurium[7,8] over BW A444U in humans, a difference which would have been difficult to anticipate on the basis of animal studies.[9,31] Consequently, the further development of atracurium is scheduled to continue while additional human studies of BW A444U are not planned at the present time.

The clinical success of BW A444U in its own right, nevertheless, does suggest that further developmental research in the area of nondepolarizing ester relaxants may yield clinically useful materials.

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