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# The Clinical Neuromuscular Pharmacology of Mivacurium Chloride (BW B1090U)

## A Short-acting Nondepolarizing Ester Neuromuscular Blocking Drug

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**Mivacurium chloride (BW B1090U), a bis-benzylisoquinolinium diester compound, was found to undergo hydrolysis *in vitro* by purified human plasma cholinesterase in a *p*H-stat titrator at 88% of the rate of succinylcholine at *p*H 7.4, 37° C and 5 μM substrate concentration. In 72 consenting ASA Physical Status I–II patients receiving nitrous oxide/oxygen-narcotic-thiopental anesthesia, the neuromuscular blocking effect of mivacurium was assessed following bolus doses from 0.03 to 0.30 mg/kg, as well as during and following continuous infusions from 35 to 324 min in length. The calculated ED95 for inhibition of adductor pollicis twitch evoked at 0.15 Hz was 0.08 mg/kg. At 0.1 mg/kg, 96% block developed, onset to maximum block required 3.8 ± 0.5 min, and recovery to 95% twitch height occurred 24.5 ± 1.6 (SE) min after injection. At 0.25 mg/kg, onset was 2.3 ± 0.3 min; 95% recovery developed within 30.4 ± 2.2 min, an increase in duration of action of only 24% *versus* 150% higher dosage. Comparative recovery indices from 5 to 95% or from 25 to 75% twitch heights did not differ significantly among all dosage groups from 0.1 to 0.3 mg/kg (range 12.9 to 14.7 and 6.6 to 7.2 min, respectively). In 38 patients who received mivacurium by *continuous infusion* (duration 88.1 ± 7.1/47.1 min, SE/SD) for maintenance of 95 ± 4% twitch inhibition, the mean 5–95% and 25–75% recovery indices after discontinuation of infusion were 14.4 ± 0.6 and 6.5 ± 0.3 min ($P > 0.5$ *vs.* all single bolus doses). The train-of-four ($T_4$) ratio, within 2.6 ± 0.5 min after 95% twitch recovery following bolus doses, averaged 79.5 ± 1.8% (n = 32). Similarly, after discontinuation of infusions, the $T_4$ ratio reached 73.4 ± 1.9% within 3.4 ± 1.9 min after 95% twitch recovery (n = 33). Antagonism of residual block was seldom indicated, but, to test ease of reversal, eight patients electively received neostigmine (0.06 mg/kg) with atropine (0.03 mg/kg) at 67 to 93 (76.6 ± 3.5) % block. Twitch returned to 95% of control within 4.5 to 9.5 (6.3 ± 0.5) min after neostigmine. Mivacurium may offer increased versatility in providing clinical muscle relaxation in a variety of situations. Further studies seem appropriate. (Key words: Antagonists: neuromuscular relaxants. Enzymes: plasma cholinesterase. Neuromuscular relaxants: mivacurium chloride.)**

OUR EFFORTS to develop a short-acting nondepolarizing neuromuscular blocking agent for clinical use have recently concentrated on the synthesis of bis-benzylisoquinolinium diester compounds which are designed to undergo hydrolysis by human plasma cholinesterase.[1]§§ The results of structure-activity correlations with two of the compounds, BW 785U§§ and BW A444U,[1] in humans and in animals (J. J. Savarese, H. A. El-Sayad, W. B. Wastila: data on file) strongly suggested a relationship between speed of hydrolysis by plasma cholinesterase *in vitro* and duration of action *in vivo*. More importantly, these observations also showed that rapid hydrolysis might be retained in selected compounds together with an increase in neuromuscular blocking potency, such that the side effect of histamine release[1]§§¶¶ might be markedly reduced.

As a result, the compound mivacurium chloride (BW B1090U, fig. 1), hereafter referred to as the cation mi-

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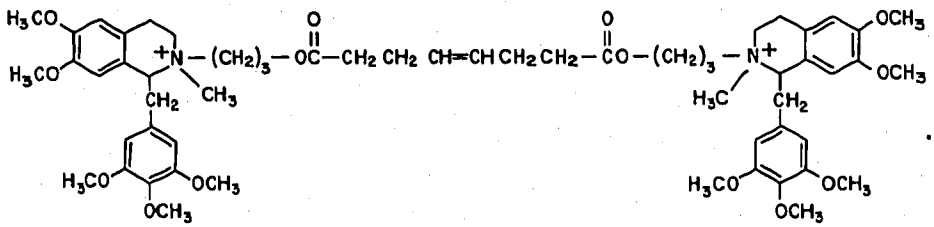
§§ Savarese JJ, Ali HH, Basta SJ, Ramsey FM, Rosow CE, Lebowitz PW, Lineberry CG, Cloutier G: Clinical neuromuscular pharmacology of BW 785U, an ultra-short-acting nondepolarizing ester neuromuscular blocking agent. Abstract. ANESTHESIOLOGY 53:S274, 1980.

¶¶ Rosow CE, Basta SJ, Savarese JJ, Ali HH, Kniffen KJ, Moss J: BW 785U: Correlation of cardiovascular effects with increase in plasma histamine. ANESTHESIOLOGY 53:S270, 1980.



**MIVACURIUM CHLORIDE**
**(BW B1090U)**

FIG. 1. Chemical formula of mivacurium chloride (BW B1090U).

vacurium, was identified as a potent short-acting nondepolarizing agent in animals.[2] The autonomic and cardiovascular safety margin was wide enough to suggest that clinical evaluation of the substance might be warranted.[2]

The purpose of the present study was the delineation of the neuromuscular blocking properties of mivacurium in human subjects. Potency, dose-response for onset and duration of action, and ability to antagonize residual block by neostigmine were to be established.

Particular attention was to be paid to demonstration of a lack of "cumulative property" in the pharmacodynamics of mivacurium, since this lack had already been noted in animals.[2] The "cumulative property" is defined herein as the relationship of rate of recovery from neuromuscular blockade to size of dose and to duration of administration of drug. For a noncumulative neuromuscular blocker, for example, the recovery rate should remain constant following a wide range of dosages, as well as following administration for widely varying time periods.

Hydrolysis by purified human plasma cholinesterase *in vitro* was measured. The relationship of the duration of neuromuscular blocking effect of mivacurium to the individual subject's plasma cholinesterase activity was evaluated.

## Materials and Methods

### Patient Preparation and Monitoring

The study was approved by the Subcommittee on Human Studies, Massachusetts General Hospital. All patients gave written informed consent for all monitoring, data collection, and anesthetic procedures.

Seventy-two ASA Physical Status I or II patients (ages 18–49 yr) were studied. Females of childbearing potential were excluded, as were any patients with a history of neuromuscular, cardiovascular, renal, or hepatic disorders. The mean patient ages and weights, ±SE/SD, were 31.1 ± 0.9/8.1 yr and 77.7 ± 1.4/12.2 kg, respectively.

On the day of the study, all subjects were given morphine (0.1–0.15 mg/kg im) and/or diazepam (0.1–0.2 mg/kg po) 1 h preoperatively. Sixteen-gauge intravenous and 20-gauge radial arterial cannulae (the latter in patients who received greater than ED95 dosage) were inserted under local anesthesia. Additional morphine and/or diazepam were given iv as necessary for adequate sedation. Anesthesia was then induced with thiopental (4–8 mg/kg) and fentanyl (4–8 μg/kg) iv in divided doses. Nitrous oxide and oxygen (4L/2L inspired mixture) were initially administered by mask. The trachea was intubated either without a relaxant, using 4% lidocaine as topical analgesia, or after paralysis induced by mivacurium. In the latter case, tracheal intubation was performed at least 5 min after the maximum neuromuscular and cardiovascular effects of mivacurium had been measured. Ventilation was controlled throughout the study to maintain arterial and/or end-tidal $P_{CO_2}$ between 35 and 45 mmHg. Esophageal temperature was kept between 34.5 and 37.5° C by warming all iv fluids, by heated humidification of inspired gases, and by adjustment of operating room temperature.

Anesthesia was continued using the same gas mixture with additional thiopental and/or fentanyl given iv as needed to minimize variation in arterial pressure and heart rate. The electrocardiogram was monitored continuously (Tektronix Model 412 or 414). At lower dosage of mivacurium (0.03, 0.05, and 0.07 mg/kg) arterial pressure was measured by oscillotonometry at 1-min intervals for 5 min before and for 10 min after administration. At dosage above the ED95 (0.1, 0.15, 0.20, 0.25, and 0.30 mg/kg), arterial pressure was measured directly. Heart rate was measured continuously by a Grass 7P44A tachograph triggered by the R-wave of the electrocardiogram or by the arterial pulse wave.

The mechanomyogram of thumb adduction was quantitated with a Grass FT10 force-displacement transducer. The single twitch of the thumb was evoked at 0.15 Hz using square-wave pulses 0.2 msec in duration, generated by a Grass S88 stimulator and applied through a stimulus isolation unit to the ulnar nerve at the wrist *via* 23-gauge steel needle electrodes placed 3 cm apart. Train-of-four ($T_4$) stimulation (2 Hz for 2 s) was applied at 5–10-min intervals during maintenance of and recovery from neuromuscular blockade. Tetanic stimulation (50 Hz for 5 s) was applied once each in five

subjects during maintenance of block by infusion and following 95% recovery of twitch. This was done as a further test of mechanism of block or adequacy of recovery.

All cardiovascular and neuromuscular measurements were recorded simultaneously on a Grass Model 7 Polygraph.

### Measurements

After a 10 min stable baseline period, mivacurium was injected as a 10–15-s bolus into a smoothly flowing iv stream. Measurements of maximal twitch depression, as well as arterial pressure and heart rate changes, were obtained before any patient stimulation (laryngoscopy or surgery) was begun. Recovery from neuromuscular blockade induced by the initial bolus dose of mivacurium was observed to at least 95% of control twitch height and usually to a $T_4$ value of 70% or more.[3] If clinical relaxation was to be maintained, a second bolus of mivacurium (0.1–0.3 mg/kg) was given to re-establish at least 95% block. This was followed by a continuous infusion, begun as soon as twitch height had returned to 5% of control, and continued at a rate sufficient to maintain 95 ± 4 (usually 95–99)% block. The infusion was discontinued as surgery was ending, and the rate of spontaneous recovery from neuromuscular blockade was measured and compared with recovery from the original bolus dose. *Duration of infusion* was calculated from administration of the *second bolus* to discontinuation of the infusion. Recovery intervals from 5 to 95% and from 25 to 75% twitch heights after various bolus doses and after infusions of mivacurium were compared to ascertain whether or not a cumulative pharmacodynamic effect was evident.

In this study, the concept of cumulative pharmacodynamics is defined as the relationship of rate of spontaneous recovery from neuromuscular blockade to size of dose and to duration of administration of drug.

### Antagonism of Neuromuscular Blockade

Antagonism of residual neuromuscular blockade was electively tested in eight individuals who received neostigmine (0.06 mg/kg) together with atropine (0.03 mg/kg) iv administered over 1 min at neuromuscular block ranging from 67 to 93% reduction of twitch height. The time from completion of injection of the antagonist mixture to recovery of twitch height to 95% of control and to $T_4$ ratio greater than 70% was measured.

### Dibucaine Number and Plasma Cholinesterase Activity

Venous or arterial samples for this determination were drawn prior to induction of anesthesia. The assays were performed according to the method of Kalow and Genest.[4]

### Hydrolysis by Plasma Cholinesterase

The rate of hydrolysis of mivacurium (relative to that of succinylcholine), as catalyzed by purified human plasma cholinesterase (E.C. 3.1.1.8), was measured *in vitro* and calculated according to a modification of the method of Kitz *et al.*[5] Experiments were done at *p*H 7.4 and 37° C, using substrates at 5-$\mu$M concentrations. Determinations for substrate pairs (mivacurium and succinylcholine) were always done on the same day, using identical batches of enzyme. Typical enzyme activities were in the range 20–40 $\mu$M acetylcholine hydrolyzed/ml/h.

### Statistics

The dose-response curve for neuromuscular blockade was estimated by linear regression of probit values corresponding to the percentage depth of neuromuscular blockade. The method of Litchfield and Wilcoxon[6] was used for this estimation, as well as for testing of parallelism of dose-response curves.

Other appropriate comparisons were made by linear regression, Student's *t* test or F-test analysis of variance.[7]

## Results

Data are given as mean ± SE or, where stated, mean ± SE/SD.

### Hydrolysis *In Vitro*

The hydrolysis rate of mivacurium *in vitro*, as catalyzed by purified human plasma cholinesterase, was 1.76 ± 0.14 $\mu$Mol/hr, or approximately 88% the rate of succinylcholine (mean ± SE of three determinations).

### Mechanism of Block

Fade of tetanic and train-of-four ($T_4$) responses, and facile antagonism by neostigmine (see below), were consistently noted at all depths of block. These observations are compatible with a non-depolarizing mechanism demonstrated in preclinical studies where no change in resting membrane potential was noted during mivacurium-induced block.***

*** Wastila WB, Savarese JJ, Wang C, White H, Everitt B, Grebe G, Soroko F: Comprehensive report on the pharmacology of BW B109OU, submitted to FDA as part of IND report, pages 34, 36, 37, dated 1/31/84.

TABLE 1. Neuromuscular Blocking Properties of Mivacurium Chloride (BW B1090U) in Patients under Nitrous Oxide/oxygen-fentanyl-thiopental Anesthesia

| Dose (mg/kg) | n | ED95 Multiple | % Twitch Inhibition ± SE | Onset Time* (Min ± SE) | Time to 95% Recovery* (min ± SE) | Time to 25% Recovery* (Clinical Duration) (min ± SE) | Recovery Indices† (Min ± SE) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 25–75% | 5–95% |
| 0.03 | 9 | 0.4 | 9.4 ± 4.5 | 5.6 ± 0.5 (n = 4) | 12.5 ± 2.5 (n = 4) | | | |
| 0.05 | 9 | 0.6 | 43.7 ± 8.1 | 5.3 ± 0.3 | 14.4 ± 2.0 | | | |
| 0.07 | 9 | 0.9 | 75.3 ± 9.4 | 4.2 ± 0.3 | 18.6 ± 2.8 | | | |
| 0.10 | 9 | 1.2 | 95.7 ± 2.8 | 3.8 ± 0.5 | 24.5 ± 1.6 | 14.2 ± 1.5 | 7.0 ± 0.5 | 12.9 ± 0.7 |
| 0.15 | 9 | 1.9 | 100 | 3.3 ± 0.2 | 26.9 ± 1.6 | 16.8 ± 1.1 | 6.6 ± 0.6 | 13.6 ± 0.9 |
| 0.20 | 10 | 2.5 | 100 | 2.5 ± 0.3 | 30.6 ± 2.4 | 19.7 ± 1.8 | 6.9 ± 0.4 | 14.7 ± 0.8 |
| 0.25 | 8 | 3.1 | 100 | 2.3 ± 0.3 | 30.4 ± 2.2 | 20.3 ± 1.5 | 6.6 ± 0.5 | 13.8 ± 0.7 |
| 0.30 | 9 | 3.8 | 100 | 1.9 ± 0.3 | 36.7 ± 4.3 | 25.0 ± 2.8 | 7.2 ± 1.2 | 14.5 ± 2.3 |
| All bolus doses combined | 45 | — | — | — | — | — | 6.8 ± 0.3 | 14.1 ± 0.6 |
| Infusions‡ | 38 | — | — | — | — | — | 6.5 ± 0.3 | 14.4 ± 0.6 |

* Measured from completion of injection.
† From 25 to 75% and from 5 to 95% twitch height. There were no significant differences.
‡ Mean Duration 88.1 ± 7.1/47.1 (SE/SD) min. Range 35–324 min.

## DOSE-RESPONSE AND DURATION

Dose-response data are summarized in tables 1 and 2. The calculated ED95 for neuromuscular blockade is 0.081 mg/kg (95% confidence limits 0.063–0.103). The ED50 is 0.052 (0.044–0.061) mg/kg.

After 0.1 mg/kg, a dose which caused 95.7% block, the duration from injection to recovery of twitch to 95% of control force was 24.5 ± 1.6 min. After 0.2 and 0.3 mg/kg, recovery occurred in 30.6 ± 2.4 and 36.7 ± 4.3 min, respectively. The increase in length of block was only 25 and 50% *versus* increases of 100 and 200% in dosage (table 1; figs. 2, 3).

The "clinical duration," *i.e.*, time from injection to return of twitch to 25% of control, varied from 14.2 ± 1.5 min after 0.1 mg/kg to 25.0 ± 2.8 min after 0.3 mg/kg (1.2 and 3.8 × ED95, respectively; table 1).

Increasing dosage of mivacurium resulted in more rapid ablation of the twitch. Onset at 0.25 mg/kg (2.3 ± 0.3 min) was 1.5 min faster than at 0.10 mg/kg (3.8 ± 0.5 min). In contrast, duration of action was only 24% longer, although dosage had been increased 150% (30.4 ± 2.3 min *vs.* 24.5 ± 1.6 min; table 1; figs. 2, 3).

Mean intervals from 5 to 95% and from 25 to 75% twitch heights ranged from 12.9 to 14.7 min and from 6.6 to 7.2 min, respectively (table 1), at all bolus dosages from 0.1 to 0.3 mg/kg. They did not differ significantly; consequently, when plotted graphically, the data show a series of apparently parallel recovery patterns (fig. 3). The mean intervals for all subjects at all single bolus doses combined were 14.1 ± 0.6 min and 6.8 ± 0.3 min, respectively (table 1).

The train-of-four ratio reached 70% or more within 1.7–3.8 min after the single twitch had returned to 95% of control following various bolus doses from 0.1 to 0.3 mg/kg (n = 32 observations, table 2). This interval, which we term the T95 → $T_4 \geq 70\%$ interval, was 2.6 ± 0.5 min when all dosage groups were combined. The latter value was subsequently compared with the corresponding combined value obtained following spontane-

TABLE 2. Comparison of Single Twitch and Train-of-four ($T_4$) Recovery after Various Doses of Mivacurium Chloride (BW B1090U⁺)

| Dose (mg/kg) | n | Mean Time* to 95% Twitch (Min) + SE | Mean Time* to $T_4 \geq 70\%$ (Min) + SE | T95 → $T_4$ ≥ 70%† (Min) + SE | Mean $T_4$ Ratio‡ ± SE Percent |
|---|---|---|---|---|---|
| 0.10 | 6 | 25.3 ± 2.3 | 28.7 ± 2.7 | 3.4 ± 0.8 | 79.2 ± 3.4 |
| 0.15 | 6 | 25.1 ± 1.6 | 28.9 ± 1.7 | 3.8 ± 0.5 | 88.5 ± 3.4 |
| 0.20 | 7 | 27.9 ± 1.4 | 30.8 ± 1.3 | 2.9 ± 0.7 | 84.6 ± 4.3 |
| 0.25 | 7 | 30.1 ± 2.0 | 32.2 ± 2.0 | 1.7 ± 0.4 | 70.1 ± 1.8§ |
| 0.30 | 6 | 29.9 ± 2.5 | 31.6 ± 2.5 | 1.7 ± 0.5 | 80.3 ± 2.5 |
| All single bolus doses combined | 32 | — | — | 2.6 ± 0.5 | 79.5 ± 1.8 |
| Infusions | 30 | — | — | 3.4 ± 0.3¶ | 73.4 ± 1.9¶ |

* From injection of Mivacurium.
† Interval between 95% twitch height and train-of-four ≥70%.
‡ At time of documentation.
§ $P < 0.05$ *vs.* all other single bolus dosages.
¶ $P < 0.05$ *vs.* all single boluses combined (all other comparisons NS).

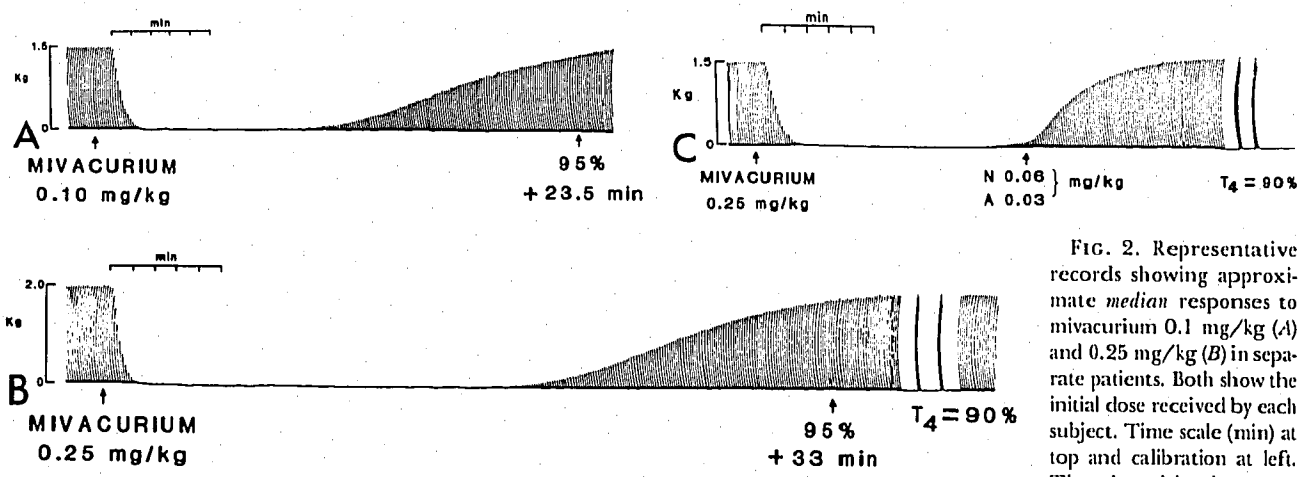



FIG. 2. Representative records showing approximate *median* responses to mivacurium 0.1 mg/kg (*A*) and 0.25 mg/kg (*B*) in separate patients. Both show the initial dose received by each subject. Time scale (min) at top and calibration at left. Thumb adduction was evoked at 0.15 Hz *via* the ulnar nerve at the wrist. At arrow, mivacurium was given iv as a bolus. $T_4$ = train-of-four stimulation (2 Hz for 2 s). In (*C*), antagonism of 93% twitch inhibition was accomplished by administration of neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg) given at arrow.

ous recovery from 30 continuous infusions of mivacurium.

## CONTINUOUS INFUSION

Spontaneous recovery from continuous infusion of mivacurium occurred at rates similar to those observed following various single bolus doses (tables 1, 2; fig. 3). Forty-four infusions were administered, ranging from 35 to 324 min in duration (mean 88.1 ± SE/SD of 7.1/47.1 min). Infusion duration was calculated from administration of the second bolus to discontinuation of infusion. In 38 of the 44, spontaneous recovery from 5% twitch height (or less) to >95% twitch height and train-of-four value > 70% was completed without antagonism of residual block by anticholinesterases. (In the six remaining individuals, residual block was *electively* antagonized with neostigmine purely as a test of reversal, not because of delayed or slow spontaneous recovery—see below.) Mean 5 to 95% and 25 to 75% recovery indices during spontaneous recovery from these infusions were 14.4 ± 0.6 and 6.5 ± 0.3 min, respectively. These data were compared with times for the same intervals from all single bolus doses (table 1). The differences were not significant ($P > 0.5$). The data show that, once recovery from mivacurium block is underway, it occurs at a rate which is independent of dose or of duration of administration at the dosages and over the range of infusions reported in this study.

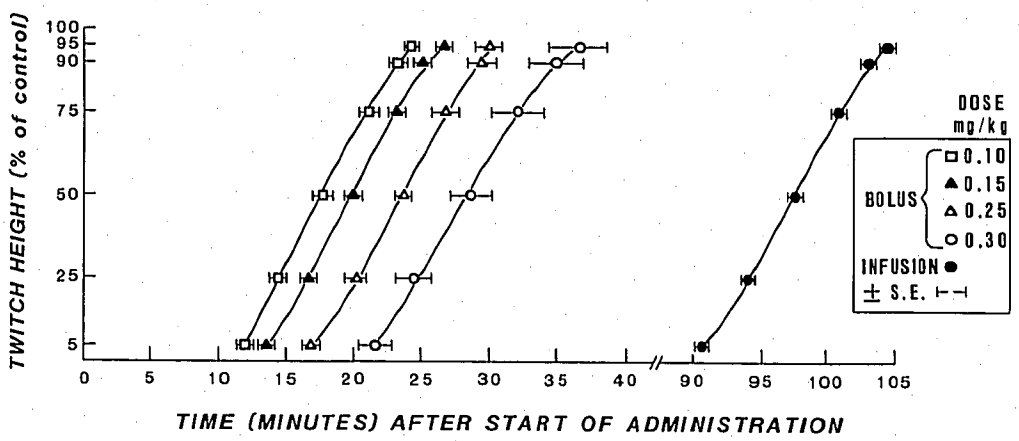



FIG. 3. Comparative mean spontaneous recovery curves of single twitch after various bolus doses and after 38 infusions of mivacurium. Mean infusion duration: 88.1 ± 7.1/47.1 min (SE/SD), range 35–324 min. Measurements are from 5 to 95% twitch recovery. Intervals from 25 to 75% and from 5 to 95% twitch recovery do not differ significantly (tables 1, 2). The data suggest that the pharmacodynamic effect of mivacurium cumulates minimally under conditions of the present study, since rate of recovery is not related to size of dose or to duration of administration.

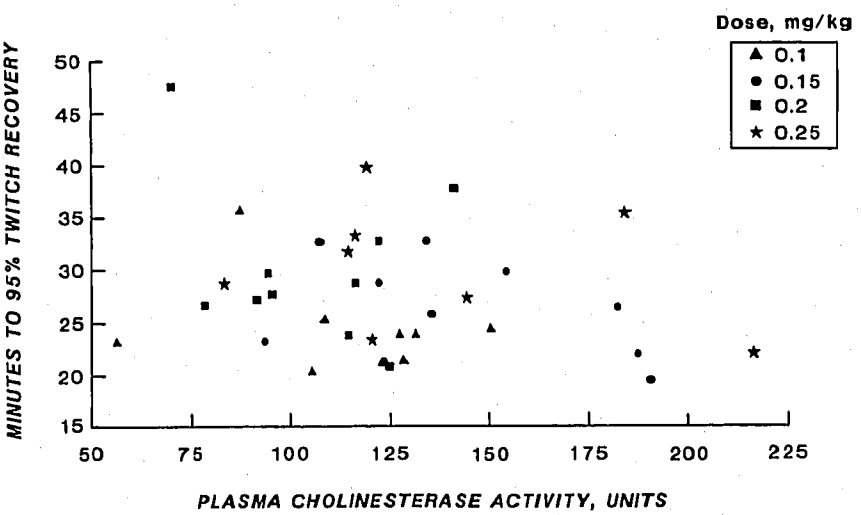



FIG. 4. Lack of correlation of plasma cholinesterase activity of individual subjects with duration of effect of mivacurium. Correlations failed to reach statistical significance at any dose. These results may suggest additional routes of metabolism and/or elimination (see text).

After discontinuation of infusion, the $T_4$ ratio reached 73.4 ± 1.9% within 3.4 ± 0.3 min (n = 30 observations) after the single twitch response had recovered to 95% of the control height (table 2). Although significantly slower ($P < 0.05$) than the mean value of 2.6 min obtained after all single bolus doses combined, this 0.8 min difference is of little clinical relevance.

### Repetitive Dosage

Eight patients received two successive 0.25-mg/kg doses of mivacurium, the second dose being given within less than 10 min after 95% twitch recovery from the first. The durations of effect for the two doses, from injection to recovery of twitch to 5% of control height, were 16.6 ± 1.3 and 19.3 ± 1.8 min, respectively ($P < 0.05$).

TABLE 3. Potency of Mivacurium, Other Nondepolarizing Relaxants, and Succinylcholine in Human Subjects

| Drug | ED95* (mg/kg) | Potency Ratio† | Molar Potency Ratio‡ |
|---|---|---|---|
| Mivacurium | 0.08 | 1.0 | 1.0 |
| BW A938U** | 0.027 | 0.34 | 0.34 |
| Vecuronium¶ | 0.056 | 0.70 | 1.3 |
| Pancuronium§ | 0.070 | 0.88 | 1.6 |
| Atracurium¶ | 0.26 | 3.1 | 3.4 |
| Metocurine§ | 0.28 | 3.5 | 5.6 |
| d-Tubocurarine§ | 0.50 | 6.2 | 10.5 |
| Succinylcholine†† | 0.20 (approx.) | 2.5 | 9.5 |

* Under balanced anesthesia, measuring force of thumb adduction at 0.1–0.15 Hz.
† Potency Ratio = drug under comparison/mivacurium.
‡ Based on molecular weight.
§ From Savarese, Ali, Antonio.[26]
¶ From Ali, Basta, Savarese, *et al.*[15]
** From Basta *et al.*[29]
†† From Miller *et al.*[22]

### Antagonism by Neostigmine

Since spontaneous recovery from mivacurium-induced block was rapid, antagonism of residual paralysis by administration of acetylcholinesterase inhibitors was rarely required. Nevertheless, to check facility of antagonism, eight subjects received neostigmine (0.06 mg/kg) together with atropine (0.03 mg/kg) at 67 to 93 (76.6 ± 3.5)% block. Reversal was induced either during recovery from infusion (n = 6) or from a bolus dose (n = 2). Antagonism to 95% of control twitch force developed within 6.3 ± 0.5 (4.5 to 9.5) min (fig. 2C). By comparison, *spontaneous* recovery from 25 to 95% twitch height following all administrations of mivacurium (bolus doses and infusions combined, n = 74) required 10.3 ± 0.5 min ($P < 0.05$).

### Correlation of Duration of Action with Individual Subject's Plasma Cholinesterase Activity

Despite evidence of rapid hydrolysis *in vitro*, there was poor correlation of the duration of action of bolus doses of mivacurium with the plasma cholinesterase activity of *individual subjects* (fig. 4). This discrepancy might be explained, at least in part, by the possible presence of other routes of metabolism and/or excretion of mivacurium, or by the relatively small variance of cholinesterase activities in this sample of normal individuals.

## Discussion

### Potency

The potency of mivacurium relative to other neuromuscular blocking substances is listed in table 3. The potency ratios may be listed as shown because the dose-response curves do not differ significantly from parallel-

ism[6] (fig. 5). Since mivacurium has a relatively high molecular weight, nearly twice as great as all other compounds listed in table 3 with the exception of BW A938U and atracurium, the *molar* potency ratios are approximately twice those calculated on a weight basis.

## Comparative Pharmacodynamics: Single Bolus Dosage

The data in table 1 suggest that the neuromuscular blocking pattern of mivacurium nearly fits criteria suggested for a 100% blocking dose of a short-acting nondepolarizing neuromuscular blocking drug: limits of up to 2 min onset (to abolition of twitch) and up to 20 min duration (to 95% recovery of twitch) were proposed.[8] For example, at about 2 × ED95 (0.15 mg/kg), mivacurium caused 100% twitch inhibition within 3.3 min with 95% recovery within 26.9 min. Onset was shortened to the 2-min range by an approximate doubling of this dosage, with an increase in duration of action of only 5–10 min (table 1). This pharmacodynamic pattern, where an increase in dose is accompanied by a disproportionately small extension of duration of effect, is unlike that of any other nondepolarizing neuromuscular blocker, with the possible exception of atracurium,[9,10] and is more like that of succinylcholine[11] than any other nondepolarizing agent.

The comparative total duration of action to 95% twitch recovery of mivacurium in the 3–4 × ED95 range is approximately twice that of succinylcholine, and 33–40% that of atracurium or vecuronium at similar dosage during "balanced" (nitrous oxide-oxygen-narcotic-barbiturate) anesthesia. For example, at 0.25 mg/kg, the mean duration of action of mivacurium was 30.4 min (table 1). Katz and Ryan reported recovery to 90% twitch height within 14.6 min after 1 mg/kg succinylcholine.[11] Scott *et al.* reported 95% twitch recovery within 69.7 to 83.1 min in four groups of patients who received 0.8 mg/kg atracurium,[12] approximately three times the ED95 reported by Ali *et al.*[13] and by Gramstad and Lilleaasen.[14] In the case of vecuronium, precise data on the duration of action of three times ED95 dosage (0.15–0.16 mg/kg) during balanced anesthesia using single twitch stimulation are not available. Agoston *et al.*,[15] however, reported 90% recovery from 0.12 mg/kg within a mean of 60.2 min during balanced anesthesia. Fahey *et al.* reported 90% recovery within 104 min after 0.14 mg/kg vecuronium during halothane anesthesia.[16] In an unpublished study, we have observed 95% recovery of the first twitch during train-of-four stimulation at 10-s intervals within 72 min after 0.15 mg/kg vecuronium given during balanced anesthesia.

While additional studies on the subject are clearly indicated, it seems that the onset of effect of mivacurium is comparable to those noted for atracurium or vecuronium at equipotent dosage. For example, onsets of 2.3 and 3.2 min have been reported for atracurium[13,17] and 3.8 and 2.7 min for vecuronium[13,15] at approximately 2 × ED95 (0.5–0.6 and 0.1–0.12 mg/kg, respectively). These data may be compared with 3.3 and 2.5 min, respectively, for mivacurium at 0.15 and 0.20 mg/kg (table 1). At atracurium dosage of 0.8 mg/kg (about 3 × ED95), Scott *et al.* reported onset as 1.7–1.8 min[12] (compare with 2.3 and 1.9 min at mivacurium dosage of 0.25 and 0.30 mg/kg, table 1). The data are comparable, since they were all obtained during recording of the single twitch at 0.1–0.15 Hz, and "onset" was considered as the period from drug injection to abolition of the evoked mechanomyographic or electromyographic response.

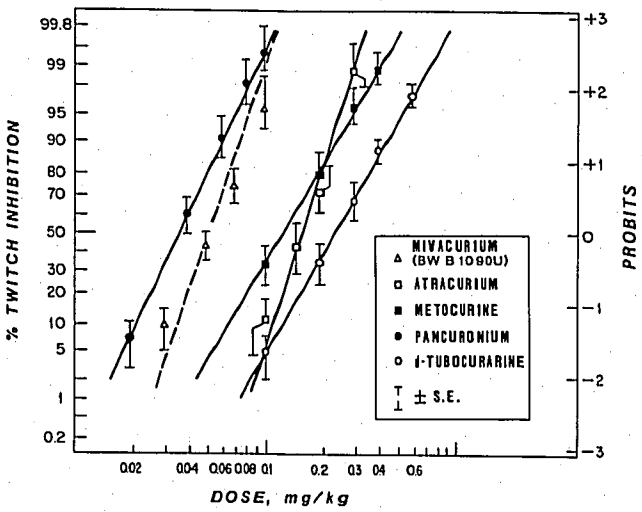



FIG. 5. Comparative dose-response curves of mivacurium, atracurium, metocurine, pancuronium, and d-tubocurarine in patients under balanced anesthesia. Data for metocurine, pancuronium, and d-tubocurarine from Savarese *et al.*[26] Data for atracurium from Ali *et al.*[13] All curves were constructed using single twitch stimulation at 0.15 Hz. They do not differ significantly from parallelism. Potency ratios are listed in table 3.

On the other hand, the onset of mivacurium, even at high dosage, is slower than that of succinylcholine.[11,18] Adjuvant maneuvers such as priming,[19,20] however, might be used to narrow the difference.

## "Noncumulative" Dynamics

While "cumulation" or lack thereof is an often-discussed aspect of the pharmacodynamics of neuromuscular blocking drugs, an adequate definition of this property does not exist. On the other hand, cumulative effect is well defined in kinetic terms as an increasing total quantity of drug within the body, usually together with an increasing pharmacological effect, sometimes associated with slower recovery, and usually corresponding

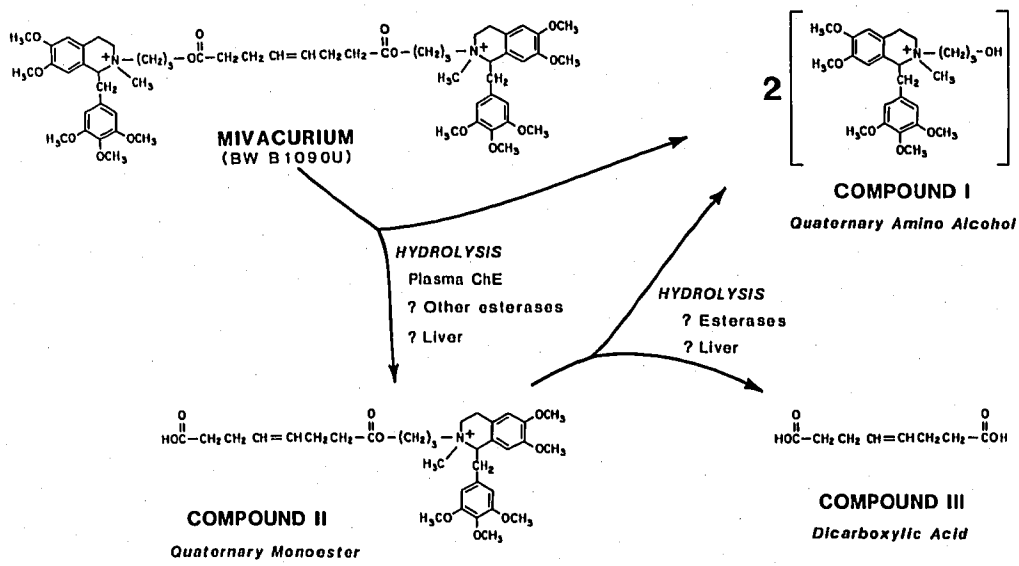



FIG. 6. Proposed metabolic pathway of mivacurium. Complete hydrolysis ultimately should yield two molecules of the quaternary amino alcohol (compound I) and one molecule of the dicarboxylic acid (compound III). The quaternary monoester (compound II) may be an intermediate or may alternatively be eliminated as an end-product. Compounds I and II have been identified in human urine. Other routes of metabolism and/or elimination of mivacurium are possible (see text).

with an increasing blood level of drug. This develops due to a rate of drug administration which is in excess of the rate of elimination by the body. As long as rate of administration remains constant, the total body store should eventually reach a plateau, or steady state, where rate of administration equals rate of elimination, and no "accumulation" exists.[21] Under these conditions, it is probably easier to show "accumulation" with drugs having relatively long half-lives.

By analogy, therefore, we suggest that *pharmacodynamic* cumulation of neuromuscular blocking drugs be defined as the relationship of rate of recovery from neuromuscular blockade (*e.g.*, 5–95% and 25–75% recovery indices) to size of dose and to duration of administration of drug. Under this definition, cumulation is inversely related to the length of the recovery indices and is directly related to any dose-dependent or time-dependent increase in these indices. Using these criteria, mivacurium shows very little cumulative property, since recovery times listed in table 1 are relatively short, and do not change over a wide dose range, nor after prolonged continuous administration by infusion, *e.g.*, for up to 5½ h. The T95 → $T_4 \geq 70\%$ intervals also remain short (table 2), emphasizing that spontaneous recovery from mivacurium-induced block proceeds rapidly to normal neuromuscular function as defined by a sensitive indicator. Another measure of lack of cumulation is the demonstration in this study of repeated relatively rapid recovery following successive administration of two large (3 × ED95) bolus doses of 0.25 mg/kg.

## METABOLISM

Rapid hydrolysis catalyzed by plasma cholinesterase may explain most of the pharmacodynamic patterns shown by mivacurium in this evaluation. For example, classical Michaelis-Menton first order kinetics may explain the surprisingly small increase in duration of effect observed as dosage is increased (table 1): it is possible that enzyme activity and speed of hydrolysis of mivacurium may increase in direct proportion to plasma concentration (dosage) of substrate (drug). Under these conditions, we may speculate that destruction of drug is fastest immediately following injection and subsequently diminishes over time, such that recovery rates (table 1) might be viewed as reflecting enzyme activity over similar ranges of diminishing drug concentrations. The disproportionately small increase in length of action as dosage is increased suggests that plasma concentrations of substrate (mivacurium) may not approach $V_{max}$ for plasma cholinesterase within the clinical dose range.

The rather poor correlation of plasma cholinesterase activity with the duration of effect of mivacurium in individual subjects (fig. 4) may at first seem surprising. This apparent discrepancy, however, may be explained by the relatively small variance of cholinesterase activities in this sample of normal individuals. An additional potentially important factor is the likelihood of other routes of metabolism and/or elimination of mivacurium (see below).

The proposed metabolic pathway of mivacurium is shown in figure 6. The breakdown products, which are pharmacologically inactive, have been identified in human urine (R. Welch, W. B. Wastila, F. DeBros, J. J. Savarese *et al.*, data in preparation).

Although pharmacokinetic studies of mivacurium in humans have not yet been completed, the relatively rapid enzymatic hydrolysis, comparatively short duration of action, and minimally cumulative dynamics which have been observed suggest comparatively rapid clearance and short elimination half-life.

Determination of the kinetics and dynamics of miva-

curium in subjects who have very low cholinesterase activity, such as individuals who are homozygotes for the atypical form of the enzyme, will, of course, be important. Since enzymatic hydrolysis is most likely the major route of clearance, the duration of action of mivacurium may be longer in these people than in normal subjects. The relative increase in duration of action, however, may not be as great as in the case of succinylcholine for three reasons: 1) the upper limit of the clinical dose range for mivacurium is likely to be in the vicinity of 3 × ED95 or 0.25 mg/kg, whereas 1 mg/kg doses of succinylcholine constitute about 4–5 × ED95,[22] and, therefore, represent a relatively greater overdose and, consequently, higher clearance load; 2) other clearance pathways in humans, such as liver uptake and/or metabolism, and renal elimination are quite possible, since these have been clearly demonstrated in the cat and dog (W. B. Wastila, R. Welch, *et al.*, data in preparation); and 3) the complicating process of phase II block cannot occur in the case of mivacurium.

## Antagonism by Neostigmine

We have previously stated our concern regarding antagonism in humans of residual block produced by nondepolarizing substances such as mivacurium which are hydrolyzed by plasma cholinesterase.[1,23] Since both this enzyme and acetylcholinesterase are inhibited by anticholinesterases,[24] the concern is that prevention of metabolism of mivacurium by anticholinesterase administration might prolong the blocking effect, rather than antagonize it. It is likely that, during reversal, hydrolysis of mivacurium may be slowed for a brief period due to a short-lasting inactivation of plasma cholinesterase.[25] Nevertheless, as previously noted with the related substances BW 785U§§ and BW A444U,[1] and as usual with other standard nondepolarizing muscle relaxants, moderate levels of mivacurium-induced block are readily antagonized by anticholinesterases, such as neostigmine, due to *acetylcholinesterase* inhibition. In fact, antagonism of mivacurium block seems at least as facile as reversal of the long-acting metocurine or the intermediate-acting atracurium (table 4) from similar depths of blockade.[9,26] Presumably, within about 20 min after neostigmine administration, plasma cholinesterase activity should have recovered sufficiently to destroy any residual mivacurium ester material.[25]

Further observations are needed to fully characterize antagonism of mivacurium-induced block, since our data from eight demonstrations constitute only a pilot study at best.

Neostigmine-induced recovery of mivacurium from about 75% block represents an acceleration of only 4.0 min (40%) *versus* the spontaneous recovery pattern. While this difference is statistically significant, in many cases, such a minor acceleration of recovery may not be clinically important. Antagonism of residual mivacurium-induced block, then, would seem necessary less frequently than following administration of other nondepolarizing agents. Further studies are needed to fully investigate the relative ease of antagonism of mivacurium-induced block in human subjects, and to better define the relative merits of spontaneous *versus* anticholinesterase-aided recovery following mivacurium administration.

TABLE 4. Comparative Antagonism of Neuromuscular Blockade

| Drug | Duration | n | % Twitch Inhibition (Range) | Neostigmine Dose (mg/kg) | Reversal Time* ± S.E. |
|---|---|---|---|---|---|
| Mivacurium | Short | 8 | 76.6 (67–93) | 0.06 | 6.3 ± 0.5 |
| Atracurium[2] | Intermediate | 4 | 75.3 (64–85) | 0.06 | 8.2 ± 1.4 |
| Metocurine[26] | Long | 6 | 79.0 (75–85) | 0.05 | 7.6 ± 0.4 |

* Minutes from neostigmine injection to return of twitch to 95–98% of control force.

## Brief History and Structure-Activity Relationship: Nondepolarizing Ester Compounds

Benzylisoquinolinium diester compounds have been known since 1961, when Brittain, Collier, and D'Arcy described the pharmacology of γ-oxalolaudonium bromide in the cat. Nondepolarizing block of brief duration was created in this substance, which bears a chemical resemblance to the long-acting drug laudexium. This was done by incorporating two ester linkages into a ten-atom chain joining two benzylisoquinolinium moieties, in order to allow the possibility of hydrolysis by esterases. The new compound was inactive in a very brief clinical trial.[27]

Three diester materials developed by our group have already been evaluated in humans: BW Y100,††† BW 785U,§§ and BW A444U.[1] The progression from these earlier materials to the new agent mivacurium represents an evolution from relatively slow to rapid hydrolysis by plasma cholinesterase, as well as a major improvement in neuromuscular blocking potency. As a result, the side effect of histamine release has been markedly diminished in mivacurium, to the point where in preliminary evaluations in healthy individuals it seems roughly similar to that of atracurium.[9,12,28]

## Conclusion

Mivacurium may constitute a versatile new addition to anesthetic practice, since its administration seems

††† Savarese JJ, Ali HH, Donlon JV, Kitz RJ: 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.

particularly adaptable to short procedures (such as in ambulatory care surgery) or to maintenance of relaxation by infusion for longer procedures where easy alteration of the depth of block and fast spontaneous recovery might be considered important. To adequately define the full potential of mivacurium in anesthetic practice, additional studies would seem indicated.

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