

## Clinical Pharmacology of GW280430A in Humans

Matthew R. Belmont, M.D.,\* Cynthia A. Lien, M.D.,† Joseph Tjan, M.D.,‡ Eleanor Bradley, C.R.N.A.,§ Brenna Stein, C.R.N.A.,§ Sanjay S. Patel, Ph.D.,|| John J. Savarese, M.D.#

**Background:** An ultrashort-acting nondepolarizing neuromuscular blocking agent that could be an alternative to succinylcholine has been the focus of a concerted effort in the field of muscle relaxants. GW280430A showed a promising pharmacodynamic profile in preclinical work and a wide margin of safety and so was selected for study in humans.

**Methods:** Thirty-one volunteers participated in this study, which determined the dose producing 95% block (ED<sub>95</sub>) and the safety and pharmacodynamics of increasing ED<sub>95</sub> multiples. Anesthesia was induced and maintained with propofol, midazolam, and fentanyl. Neuromuscular transmission was measured at the adductor pollicis using ulnar nerve stimulation, and responses were recorded continuously by standard mechanomyographic monitoring.

**Results:** The ED<sub>95</sub> for GW280430A is 0.19 mg/kg. The time to onset of 90% block ranged from 1.3 to 2.1 min, depending on the dose. Clinical durations ranged from 4.7 to 10.1 min and increased with increasing dose. Five to 95% and 25–75% recovery rates were approximately 7 and 3 min, respectively, and were independent of the dose administered. Transient cardiovascular side effects were observed at doses beginning at 3 × ED<sub>95</sub> and above and were suggestive of histamine release. Most volunteers receiving 4 × ED<sub>95</sub> exhibited plasma histamine concentrations indicative of significant histamine release.

**Conclusions:** GW280430A has a rapid onset and ultrashort duration of action. The recovery rate is rapid, predictable, and independent of dose. Doses at least up to 2.5 × ED<sub>95</sub> seem to be free of side effects and seem to be able to provide relaxation within 60–90 s.

NEUROMUSCULAR blocking agents' use and utility in surgical anesthesia have been well established over many years. After Savarese and Kitz<sup>1</sup> identified the need for novel short-, intermediate-, and long-acting nondepolarizing neuromuscular blockers without significant side effects or accumulation, we have seen the introduction of many new agents. The long-acting doxacurium and

pipecuronium; the intermediate-acting atracurium, vecuronium, rocuronium, and cisatracurium; and the short-acting mivacurium and rapacuronium have all been added to our armamentarium of neuromuscular blockers (NMBs). Rapacuronium was promising as an alternative to succinylcholine when it was introduced in 1999 because of the profound relaxation it provided in 60 s. Unfortunately, widespread use of rapacuronium was associated with reports of severe bronchospasm, and the drug was withdrawn from the market in 2001. Therefore, an ultrashort-acting nondepolarizing alternative to succinylcholine has continued to be a focus of concerted efforts in this field. The clinical use of succinylcholine is associated with several undesirable side effects specific to the depolarizing nature of the block it produces.<sup>2</sup> The most common side effects are myalgias and increased intraocular pressure. In addition, hyperkalemia, bradycardia, and increased intragastric and intracranial pressures can be seen.<sup>3</sup> Moreover, because succinylcholine is primarily hydrolyzed by plasma cholinesterase, it is not used in patients who have reduced activity or deficiency of this enzyme. Nevertheless, succinylcholine continues to be used because of its unique properties of a very rapid onset combined with an ultrashort duration of action. GW280430A is one of several new enantiomeric bisquaternary compounds evaluated in several pharmacologic assays that indicated a rapid onset and ultrashort duration. Based on the pharmacodynamic profile from experiments in monkeys, cats,<sup>4</sup> and dogs,<sup>5</sup> which showed a rapid onset and offset of neuromuscular block and a wide safety margin with respect to cardiovascular side effects, it was selected for study in humans. On this basis, GW280430A seems to have the unique time profile of succinylcholine without the side effects inherent to a depolarizing NMB. This investigation of the safety and efficacy of GW280430A was therefore performed to establish its neuromuscular blocking potency and pharmacodynamic profile in adult male volunteers under general anesthesia.

### Materials and Methods

The Institutional Review Board of Weill Cornell Medical Center (New York, New York) approved this open-label ascending-dose study of GW280430A administered by bolus injection into healthy male volunteers aged 18–59 yr, within 30% of ideal body weight, during nitrous oxide–oxygen–opioid–propofol anesthesia. A total of 31 subjects participated in this study after giving

This article is accompanied by an Editorial View. Please see: Caldwell JE: The continuing search for a succinylcholine replacement. ANESTHESIOLOGY 2004; 100:763–4.

\* Associate Professor of Anesthesiology, † Professor of Anesthesiology, ‡ Assistant Professor of Anesthesiology, # Professor of Anesthesiology and Chairman, New York Presbyterian-Weill Cornell Medical Center. § Certified Registered Nurse Anesthetist, New York Presbyterian Hospital. || Director, Clinical Research, Avera Pharmaceuticals, Incorporated, San Diego, California.

Received from the Department of Anesthesiology, Weill Medical College of Cornell University, New York Presbyterian Hospital-Cornell, New York, New York. Submitted for publication January 31, 2003. Accepted for publication May 20, 2003. Supported by GlaxoWellcome Company, Research Triangle Park, North Carolina. Dr. Savarese was a consultant to GlaxoWellcome at the time this study was performed.

Address reprint requests to Dr. Belmont: Weill Medical College of Cornell University and New York Presbyterian Hospital, 525 East 68th Street, New York, New York 10021. Address electronic mail to: mab2012@med.cornell.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

**Table 1. Dose Schedule Assignment for Subjects in Groups C–G**

Group*	No. of Subjects	No. of Bolus Doses per Subject	Bolus Dose Number†		
			1	2	3
C	4	2	0.18 mg/kg (ED <sub>95</sub> )	0.36 mg/kg (2 × ED <sub>95</sub> )	—
D	4	2	0.36 mg/kg (2 × ED <sub>95</sub> )	0.54 mg/kg (3 × ED <sub>95</sub> )	—
E	4	2	0.72 mg/kg (4 × ED <sub>95</sub> )	0.9 mg/kg (5 × ED <sub>95</sub> )	—
F	4	3	0.45 mg/kg (2.5 × ED <sub>95</sub> )	0.3 mg/kg (1.7 × ED <sub>95</sub> )	0.3 mg/kg (1.7 × ED <sub>95</sub> )
G	4	3	0.54 mg/kg (3 × ED <sub>95</sub> )	0.4 mg/kg (2.2 × ED <sub>95</sub> )	0.4 mg/kg (2.2 × ED <sub>95</sub> )‡

The original dose schedule assignment of groups was based on the preliminary ED<sub>95</sub> calculated from groups A and B.

\* The magnitudes of doses in these groups were determined from cross-subject ED<sub>95</sub> value calculated from data of groups A and B. † A period of at least 30 min (estimated to be approximately 10 half-lives) elapsed between each successive dose of GW280430A. ‡ Neuromuscular block in all subjects was reversed (edrophonium + atropine) after evidence of at least 10% T1 twitch recovery from administration of this dose.

informed consent. The first part (groups A and B) was performed to determine an approximate ED<sub>95</sub> dose in 11 subjects. Subject 1 was to be given an initial dose of 0.02 mg/kg followed by an estimated dose that would produce 50% block (ED<sub>50</sub>). A lack of response from the initial 0.02 mg/kg dose would lead to a doubling of each successive dose until some twitch suppression was observed. The ED<sub>50</sub> dose was based on a log-probit analysis with a historic slope estimate of 7.0 (based on a log-probit transformation, where the dose was log transformed and the response was transformed with the probit function). Subject 2 was to be given three doses of estimated ED<sub>25</sub>, ED<sub>50</sub>, and ED<sub>75</sub>. Subject 3 was to be given doses of estimated ED<sub>50</sub>, ED<sub>75</sub>, and ED<sub>90</sub>. Group B, subjects 4–11, received doses of estimated ED<sub>25</sub>, ED<sub>50</sub>, ED<sub>75</sub>, and ED<sub>90</sub>. Data were sequentially reviewed and summarized at the completion of each group. An estimated ED<sub>95</sub> was generated on site with SAS 6.08 software (SAS Institute Inc., Cary, NC) after the completion of the group A subjects, 1–3. A more accurate estimate of ED<sub>95</sub> was generated after the completion of group B subjects, 4–11, with WinNonLin software (SAS Institute Inc.). The second part (groups C–G) was performed to evaluate the safety and pharmacodynamics of ascending multiples of ED<sub>95</sub> doses in 20 volunteers, including reversal in one group (G) (table 1). The pharmacodynamic profile of GW280430A was determined at the adductor pollicis during the study.

Anesthesia was induced intravenously with midazolam (0.01–0.05 mg/kg), fentanyl (2–8 µg/kg), and propofol (2.0–2.5 mg/kg) and was maintained with nitrous oxide (70%), oxygen (30%), and propofol (50–200 µg · kg<sup>-1</sup> · min<sup>-1</sup>) in all subjects. Electrocardiogram, pulse oximetry, and temperature were monitored and maintained within normal limits. Volunteers' tracheae were intubated without use of a muscle relaxant at least 20 min before a dose of GW280430A was administered. The study drug was injected over 5 s into a rapidly running intravenous line. Blood pressure (BP; systolic, diastolic, and mean *via* radial arterial line) and heart rate (HR) were recorded continuously throughout the study to assess hemodynamic safety.

The onset, duration, and depth of neuromuscular block were assessed at the adductor pollicis using standard mechanomyographic neuromuscular monitoring techniques in all parts of the study. Neuromuscular transmission at the adductor pollicis was monitored using the evoked response to electrical stimulation of the ulnar nerve at the wrist. Supramaximal twitch stimulation (single 0.2-ms square wave) was delivered *via* surface electrodes to the ulnar nerve every 6.7 s (0.15 Hz). The evoked responses were recorded continuously on a polygraph *via* mechanomyography using a force displacement transducer attached to the thumb. A baseline of at least 20 min duration was established before a dose of the test drug was given. On evidence of beginning twitch recovery, the stimulation mode was changed from single twitch to train-of-four (TOF) every 10 s. Subsequent doses were given after at least 30 min after full neuromuscular recovery (fourth twitch to first twitch ratio ≥ 0.9) from the previous dose. Eight volunteers were also stimulated using TOF stimulation from baseline through recovery for two doses as a comparison of the effect of mode of stimulation on onset times at the adductor pollicis. Four subjects who received two doses of 0.40 mg/kg were pharmacologically reversed with 0.5 mg/kg edrophonium with 0.10 mg/kg atropine after the second dose for comparison of recovery times.

The nonlinear model examined was a two-staged, nonlinear, repeated-measures model where the dependent variable was the T1 suppression response and the independent variable was the dose. An estimate of the ED<sub>95</sub> dose was computed for each subject in groups A and B, from each of the individual dose–response curves, and a composite ED<sub>95</sub> estimate was taken by averaging these ED<sub>95</sub> estimates. The software WinNonLin was used to fit the nonlinear models.

Arterial blood samples (5 ml each) for the determination of histamine concentration in plasma were collected immediately before and at 2 and 5 min after each dose in all groups. Clinically significant histamine release was defined as a doubling from baseline and greater than 1,000 pg/ml.

**Table 2. Maximum T<sub>1</sub> Suppression ED<sub>95</sub> Modeling Results (Nonlinear Model)**

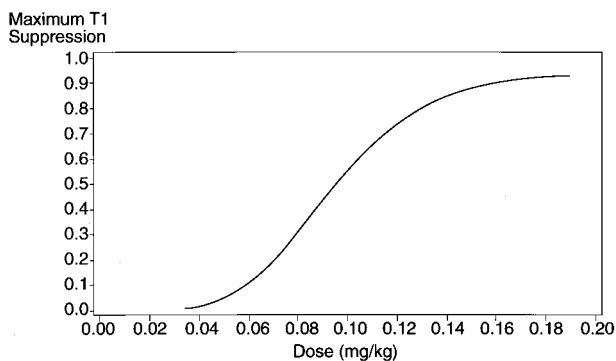
Subject No. (n = 11)	ED <sub>95</sub> , mg/kg
361	0.180
362	0.233
363	0.213
364	0.132
365	0.191
366	0.219
367	0.266
368	0.143
369	0.199
370	0.184
371	0.131
Average	0.190
SE (ED <sub>95</sub> )	0.0135
95% CI (ED <sub>95</sub> )	0.161–0.219

Final data analysis of the data from groups A and B for ED<sub>95</sub> determination.  
CI = confidence interval.

## Results

### ED<sub>95</sub>

Subject 1 received three doses, 0.02, 0.04, and 0.08 mg/kg, because the first dose produced no block. Subject 2 received 0.05, 0.065, and 0.10 mg/kg. Subject 3 received 0.08, 0.10, and 0.13 mg/kg. Subjects-11 received 0.06, 0.09, 0.12, and 0.19 mg/kg. The ED<sub>95</sub> initial estimate from the nonlinear regression model using the data from the first 11 subjects was  $0.18 \pm 0.015$  mg/kg,



**Fig. 1. Maximum T<sub>1</sub> suppression versus dose for the first 11 volunteers, graphically averaged.**

**Table 3. Neuromuscular Blocking Profile: Time to Onset (Subjects in Groups C–G)**

	0.18 mg/kg (n = 4)	0.30 mg/kg (n = 4)	0.36 mg/kg (n = 8)	0.40 mg/kg (n = 4)	0.45 mg/kg (n = 4)	0.54 mg/kg (n = 8)	0.72 mg/kg (n = 4)
ED <sub>95</sub> multiple	1.0	1.7	1.9	2.2	2.5	3.0	4.0
Time to maximum T <sub>1</sub> suppression, min							
Mean	2.6	1.4	1.7	1.5	1.6	1.5	1.5
SD	0.3	0.2	0.2	0.3	0.3	0.2	0.3
Min, max	2.3, 3.0	1.1, 1.6	1.4, 2.0	1.3, 1.9	1.3, 1.8	1.2, 1.8	1.0, 1.8
Time to 90% T <sub>1</sub> suppression, min							
No.	4	1	8	0	1	3	2
Mean	2.1	1.1	1.3		1.6	1.3	1.3
SD	0.6		0.2			0.2	0.2
Min, max	1.5, 3.0		1.0, 1.6			1.1, 1.5	1.1, 1.4

Onset times of increasing doses of GW280430A with single-twitch stimulation shows faster onset with increasing dose.

**Table 4. Neuromuscular Blocking Profile: TOF Time to Onset (Groups F and G, Third Dose)**

	0.30 mg/kg (n = 4)	0.40 mg/kg (n = 4)
Time to maximum T <sub>1</sub> suppression, min		
No.	4	4
Mean	1.2	1.0
SD	0.1	0.3
Min, max	1.1, 1.3	0.7, 1.5

Times to onset of two doses of GW280430A using train-of-four (TOF) stimulation show shorter onset times than with single twitch.

and this value was used to compute the doses for subjects in groups C–G. The ED<sub>95</sub>s from the final data were actually  $0.19 \pm 0.014$  mg/kg (table 2). Figure 1 displays the average dose–response relation.

### Onset

The time to onset of maximum block at the adductor pollicis ranged from  $2.6 \pm 0.3$  min to  $1.5 \pm 0.3$  min for doses ranging from 0.18 mg/kg (ED<sub>95</sub>) to 0.72 mg/kg ( $4 \times$  ED<sub>95</sub>). Time to 90% block for these doses ranged from  $2.1 \pm 0.7$  min to  $1.3 \pm 0.2$  min (table 3). Neuromuscular block onset data using TOF stimulation was collected at the 0.30- and 0.40-mg/kg doses. This method of stimulation yielded the shorter onsets of 1.2 and 1.0 min for these doses, respectively, compared with single-twitch onset data (table 4).

### Duration

The duration of neuromuscular block increased with increasing dose. Clinical and total durations were 4.7–10.1 min and 9.9–16.1 min, respectively, for doses of 0.18–0.72 mg/kg (table 5). Times to return of TOF of 70% or greater and 90%, with means and ranges for each dose, are also shown in table 5.

### Recovery Rates

Fire to 95% and 25–75% recovery rates were approximately 7 and 3 min, respectively, for all doses of GW280430A studied and did not increase with increasing dose (table 6).

**Table 5. Neuromuscular Blocking Profile: Duration and Recovery Rates after Bolus Dosing**

	0.18 mg/kg (n = 4)	0.30 mg/kg (n = 4)	0.36 mg/kg (n = 8)	0.40 mg/kg (n = 4)	0.45 mg/kg (n = 4)	0.54 mg/kg (n = 8)	0.72 mg/kg (n = 4)
Time from injection to 25% T1 recovery, min							
No.	4	4	8	4	4	7	3
Mean	4.7	8.6	7.0	8.9	9.8	9.3	10.1
SD	0.4	1.3	0.5	1.5	2.1	1.5	1.9
Min, max	4.3, 5.3	7.5, 9.8	6.3, 7.6	7.1, 10.4	7.8, 11.9	7.9, 12.3	8.4, 12.1
Time from injection to 95% T1 recovery, min							
No.	4	4	8	4	4	8	4
Mean	9.9	15.2	12.2	15.5	15.8	15.2	16.1
SD	1.3	3.2	1.0	3.4	3.7	2.9	2.1
Min, max	8.3, 11.4	12.5, 19	11.0, 14.3	11.8, 19.8	12.6, 21.0	11.6, 21.3	13.3, 18.2
Time from injection to T4:T1 ≥ 0.7, min							
No.	4	4	8	4	4	8	4
Mean	8.4	12.2	10.3	12.3	13.7	12.9	13.7
SD	0.5	1.5	0.7	2.5	2.3	2.0	1.7
Min, max	7.9, 9.0	10.6, 13.5	9.5, 11.4	9.3, 14.9	11.3, 15.7	10.7, 16.8	11.7, 15.8
Time from injection to T4:T1 ≥ 0.9, min							
No.	4	4	8	4	4	8	4
Mean	9.8	14.0	11.9	14.3	15.4	14.6	15.1
SD	0.7	2.6	1.2	3.6	3.1	2.7	1.8
Min, max	8.8, 10.3	11.9, 17.5	10.4, 13.5	10.2, 18.5	12.2, 19.3	11.3, 20.0	12.9, 17.2

Duration increases with increasing dose from 1–4 × ED<sub>95</sub>.

**Reversal**

Four subjects who received 0.40 mg/kg GW280430A were given 0.5 mg/kg edrophonium plus 10 µg/kg atropine at 10% T1 recovery. The total duration, the time from injection to 95% T1 recovery, and the recovery time to TOF 70% were shortened to 5.7 ± 1.1 and 2.1 ± 0.6 min, respectively. These values are compared with the times from spontaneous recovery in table 7.

**Cardiovascular Safety**

There was very little change from baseline for mean HR, mean BP, systolic BP, and diastolic BP in the first 5 min after the administration of the study drug up to and including a dose of 0.45 mg/kg (2.4 × ED<sub>95</sub>). However, at a dose of 0.54 mg/kg and above, there was some

evidence of a mean increase in HR. A mean decrease in mean arterial pressure of 17% was evident at a dose of 0.72 mg/kg. The duration of the BP decrease was less than 5 min and was self-limited (figs. 2 and 3). Figure 4 graphically plots simultaneous HR and mean arterial pressure maximal changes for each patient within the 5 min after the dose. Most of the large changes are in the upper left-hand quadrant, suggestive of typical histamine-related effects observed at high doses.

**Histamine**

Plasma histamine concentrations were determined at baseline and 2 and 5 min as described. One subject who received 0.54 mg/kg and three subjects of four who received 0.72 mg/kg exhibited 2-min postinjection

**Table 6. Neuromuscular Blocking Profile: Recovery Rates after Bolus Dosing**

	0.18 mg/kg (n = 4)	0.30 mg/kg (n = 4)	0.36 mg/kg (n = 8)	0.40 mg/kg (n = 4)	0.45 mg/kg (n = 4)	0.54 mg/kg (n = 8)	0.72 mg/kg (n = 4)
Interval 5–95%, min							
No.	3	4	8	4	4	8	4
Mean	6.5	7.8	6.4	7.6	7.2	6.9	7.1
SD	0.8	1.9	0.9	2.3	2.8	1.7	1.2
Min, max	6.0, 7.5	6.4, 10.4	5.2, 8.1	5.5, 10.8	4.8, 11.3	4.8, 10.5	5.9, 8.4
Interval 25–75%, min							
No.	4	4	8	4	4	7	3
Mean	2.7	3.3	2.5	3.4	3.1	3.0	3.2
SD	0.5	0.9	0.3	1.2	1.2	1.1	1.1
Min, max	1.9, 3.1	2.4, 4.2	1.9, 3.0	2.2, 5.1	2.3, 4.8	2.2, 5.3	2.1, 4.2
Interval 25%–T4:T1 ≥ 0.9, min							
No.	4	4	8	4	4	7	3
Mean	5.1	5.4	4.9	5.4	5.6	5.0	5.2
SD	1.1	1.5	1.1	2.1	1.8	1.6	0.8
Min, max	3.5, 6.0	4.4, 7.7	3.5, 6.7	3.1, 8.1	4.3, 8.1	3.4, 7.7	4.5, 6.1

Recovery intervals do not change with increasing dose from 1–4 × ED<sub>95</sub>.

**Table 7. Neuromuscular Blocking Profile Reversal Summary: Duration and Recovery Rates after Bolus Dosing (Part 1, Subjects in Group G)**

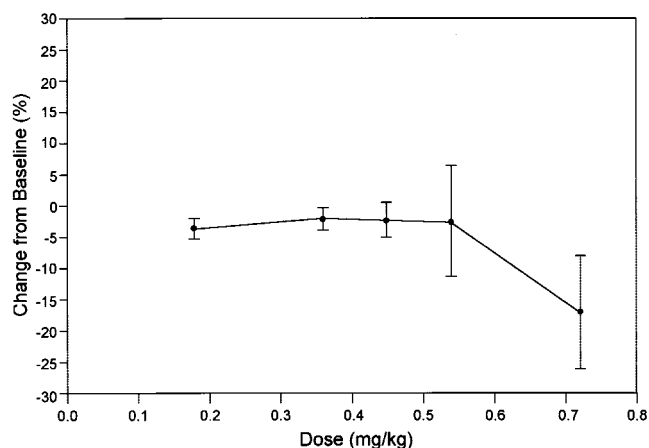
	0.40 mg/kg Reversal (n = 4)	0.40 mg/kg Nonreversal (n = 4)
Time from injection to 95% T1 recovery, min		
No.	4	4
Mean	5.7	15.5
SD	1.1	3.4
Min, max	4.3, 6.6	11.8, 11.9
Time from injection to T4:T1 $\geq 0.9$ , min		
No.	4	4
Mean	3.8	14.3
SD	1.5	3.6
Min, max	2.1, 5.7	10.2, 18.5

Reversal with edrophonium at 10% recovery speeds full recovery.

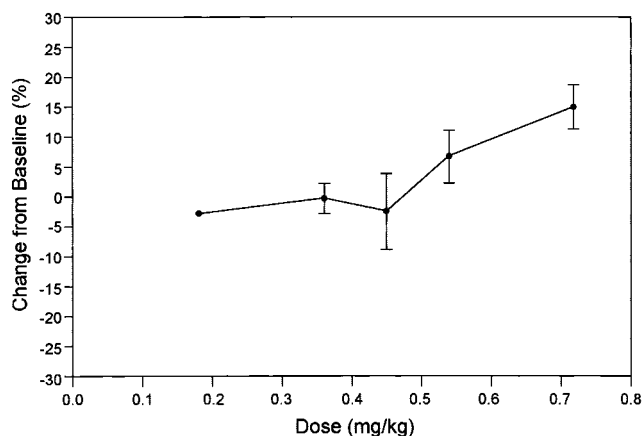
plasma histamine concentrations that were more than a doubling of baseline value and more than 1,000 pg/ml, indicative of clinically relevant histamine release. In all of these individuals, HR and BP changes and facial flushing were associated with these increases in plasma histamine (table 8).

## Discussion

The need for a nondepolarizing replacement for succinylcholine prompted the clinical investigation of GW280430A after animal studies identified it as a promising candidate. This study showed that the ED<sub>95</sub> of GW280430A in man is 0.19 mg/kg and that it has a rapid onset and ultrashort duration of action. The spontaneous recovery rate of GW280430A is rapid, predictable, and independent of dose. Edrophonium facilitated reversal, shortened duration by approximately two thirds, and was used because of its faster onset than neostigmine. An ideal ultrashort-acting nondepolarizing NMB must



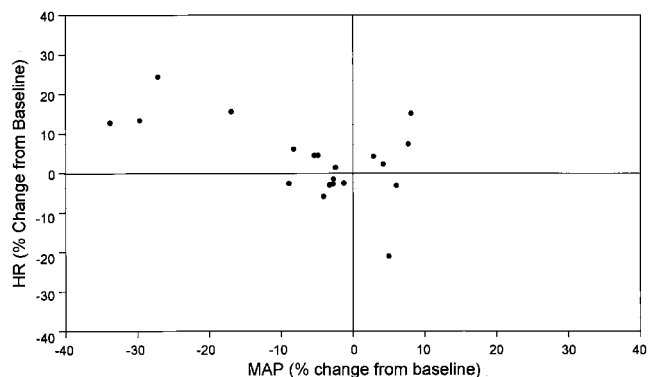
**Fig. 2.** Average maximum change from baseline mean arterial pressure is small for doses through 0.72 mg/kg.



**Fig. 3.** Average maximum change from baseline heart rate increases as dose goes above 0.45 mg/kg.

have an onset time of 60–90 s to allow comparably acceptable intubating conditions to succinylcholine. A clinical duration of approximately 10 min is also desirable. The doses of GW280430A that fit this onset profile are 0.45–0.54 mg/kg, with clinical durations of action less than 10 min. The absence of significant side effects at doses allowing reliable, rapid intubation with conditions similar to those of succinylcholine is considered an important criterion for its replacement. In this small sample, it seems that doses up to and including 0.45 mg/kg are free of side effects. Doses at or above 0.72 mg/kg caused transient side effects in most volunteers. Further studies must be performed to determine a reliable dose that has the potential of meeting all the necessary criteria for rapid tracheal intubation and that is free of significant side effects. Pharmacodynamically, it is likely that this dose will be in the range of 0.50 mg/kg. Because the dose of 0.54 mg/kg given in this study caused histamine release in one of four patients, the side effect profile must be elucidated further.

The doses of rapacurium that had been used for rapid tracheal intubation, 1.5–2.0 mg/kg, yielded clinical durations of 15–20 min, similar to mivacurium.<sup>6,7</sup> We looked at the onset and recovery of 1.5 mg/kg rapacu-



**Fig. 4.** Graphic representation of maximum changes in heart rate (HR) and mean arterial pressure (MAP) for individuals receiving a first dose of GW280430A.

**Table 8. Summary of Potential Histamine-related Side Effects of First Dose (Typified by Decrease in MAP, Increase in HR and Cutaneous Flushing)**

Dose, mg/kg	Subject No.	Maximum Change		Clinically Significant Histamine*	Drug-related Adverse Events
		MAP	HR		
0.54	392	-29.6%	+13.3%	Y	Hypotension
0.72	381	-33.8%	+12.7%	Y	Flushing of face and neck
0.72	382	-27.0%	+24.5%	Y	Hypotension Flushing of face and neck
0.72	383	-16.9%	+15.5%	Y	Hypotension Cutaneous flushing

When histamine release was clinically significant, mean arterial pressure (MAP) and heart rate (HR) were affected in the usual way, and flushing was usually observed.

\* Protocol defined this as more than a doubling of the baseline concentration and an increase to 1,000 pg/ml or more.

ronium in 35 patients under identical experimental conditions and found the onset at the adductor pollicis at 0.15 Hz to be  $1.6 \pm 0.5$  min and recovery to 90% TOF to be within  $44.2 \pm 11.4$  min without reversal and  $31.3 \pm 13.9$  min with reversal.<sup>8</sup> Rapacuronium can produce decreased BP and bronchospasm, with or without concomitant histamine release. Rapid administration of rapacuronium can produce a decrease in mean arterial pressure when administered in doses from 1 to 3 mg/kg, and patients in whom bronchospasm develops over this dose range had no correlation with histamine concentrations.<sup>9</sup> It was removed from the market because of these side effects in 2001.

Another potential advantage of GW280430A exists in its lack of accumulation as implied by the identical recovery rates independent of dose in the range of  $1-4 \times ED_{95}$  seen in this study. This is in contrast to rapacuronium, which, either because of its metabolite or its own pharmacokinetics, changes its time course characteristics from that of a short-acting agent to that of an intermediate-duration NMB after an infusion as short as 1 h.<sup>10</sup> The 25-75% recovery index for GW280430A reported here, 3 min, is the shortest reported for any nondepolarizer to date. This compares favorably with the 9 min that had been reported for rapacuronium, which placed its recovery profile between the short-acting mivacurium, 7 min, and the intermediate-acting cisatracurium, 14 min.<sup>7,10-12</sup> The time to full recovery to 90% TOF is also the shortest reported for any nondepolarizer, and this may be critically important in the ambulatory setting.

In conclusion, this study showed that this new bisquaternary compound, GW280430A, has the most promising pharmacodynamic profile to date of a nondepolarizing NMB to be considered as a replacement for succinylcholine. Doses in the  $2.5-3 \times ED_{95}$  range showed maximum block onsets within 90 s, clinical durations of less than 10 min, and complete recovery to TOF of 90% or greater within 15 min. Doses in this range may be able to be used when a rapid-sequence induction is necessary and securing of the airway must be at-

tempted within 60 s. The side effects in this small study were limited in this dose range. An ideal dose, balancing the need of rapid onset with the safety of minimal to absent side effects, should be more carefully studied. Intubation studies in patients must be performed with real induction sequences as well as studies investigating continuous infusions of this drug that should allow for continuous profound neuromuscular block with a rapid recovery.

The authors thank Benjamin Duncan, Ph.D. (Statistician, GlaxoWellcome Company, Research Triangle Park, North Carolina), for his statistical analyses, and JoAnn Rush (Administrative Assistant, Department of Anesthesiology, Weill Medical College of Cornell University, New York, New York) for her technical assistance with this manuscript.

## References

- Savarese JJ, Kitz RJ: Does clinical anesthesia need new neuromuscular blocking agents? *ANESTHESIOLOGY* 1975; 42:236-9
- Belmont MR: Succinylcholine/suxamethonium. *Curr Opin Anesthesiol* 1995; 8:362-6
- Mahajan RP: Is suxamethonium now obsolete? *Curr Anaesth Crit Care* 1996; 7:289-94
- Savarese JJ, Belmont MR, Hashim MA, Mook RA Jr, Boros EE, Samano V, Patel SS, Feldman PL, Schultz J-AI, McNulty M, Spitzer T, Cohn DL, Morgan P, Wastila WB: Preclinical pharmacology of GW280430A (AV430A) in the rhesus monkey and in the cat: A comparison with mivacurium. *ANESTHESIOLOGY* 2003; 100:000-000
- Heerd P, Kang R, The A, Hashim M, Mook R, Savarese J: Cardiopulmonary effects of the novel neuromuscular blocking drug GW280430A in dogs. *ANESTHESIOLOGY* 2003; 100:000-000
- Kahwaji R, Bevan D, Bikhazi G, Shanks C, Fragen R, Dyck J, Angst M, Matteo R: Dose-ranging study in younger adult and elderly patients of Org 9487, a new, rapid-onset, short-duration muscle relaxant. *Anesth Analg* 1997; 84:1011-8
- Savarese J, Ali H, Basta S, Embree P, Scott R, Sander N, Weakley J, Wastila W, El-Sayad H: The clinical neuromuscular pharmacology of mivacurium chloride (BW1090U). *ANESTHESIOLOGY* 1988; 68:723-32
- Belmont MR, Lien CA, Savarese JJ: Neuromuscular blocking properties of rapacuronium at the adductor pollicis and larynx. *ANESTHESIOLOGY* 2001; 95:A998
- Levy J, Pitts M, Thanopoulos A, Szlam F, Bastian R, Kim J: The effects of rapacuronium on histamine release and hemodynamics in adult patients undergoing general anesthesia. *Anesth Analg* 1999; 89:290-5
- Van den Broek L, Wierda J, Smeulders N, Proost J: Pharmacodynamics and pharmacokinetics of an infusion of Org 9847, a new short-acting steroidal neuromuscular blocking agent. *Br J Anaesth* 1994; 73:331-5
- Szenohradszky J, Caldwell J, Wright P, Brown R, Lau M, Luks A, Fisher D: Influence of renal failure on the pharmacokinetics and neuromuscular effects of a single dose of rapacuronium bromide. *ANESTHESIOLOGY* 1999; 90:24-35
- Belmont MR, Lien C, Quessy S, Abou-Donia M, Abalos A, Eppich L, Savarese J: The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *ANESTHESIOLOGY* 1995; 82: 1139-45