The Clinical Neuromuscular Pharmacology of 51W89 in Patients Receiving Nitrous Oxide/Opioid/Barbiturate Anesthesia

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Background: Atracurium is a mixture of ten stereoisomers. 51W89, one of these isomers, is a potent nondepolarizing intermediate-duration neuromuscular blocking agent. Preclinical studies have shown 51W89 to be significantly more potent than atracurium but with a similar neuromuscular blocking profile. This study was undertaken to establish the neuromuscular blocking potency and pharmacodynamics of 51W89 in patients undergoing elective surgical procedures.

Methods: Ninety-nine ASA physical status 1 or 2 patients undergoing elective surgical procedures under nitrous oxide/opioid/barbiturate anesthesia were studied. The neuromuscular blocking effect of 51W89 was assessed after administration of bolus doses from 0.015 to 0.4 mg/kg, as well as during and after continuous infusions from 11 to 249 min in length.

Results: The calculated ED50 for inhibition of adductor pollicis twitch evoked at 0.15 Hz was 0.048 mg/kg. At 0.10 mg/kg, maximum block developed within 5.2 ± 0.3 min, and recovery to 95% twitch height occurred 64.4 ± 3.9 min after injection. At 0.4 mg/kg, onset was 1.9 ± 0.1 min, and 95% recovery developed within 121.0 ± 5.9 min. Comparative recovery indexes from 5% to 95% or from 25% to 75% twitch heights did not differ significantly among all dosage groups from 0.1 to 0.4 mg/kg (means ranged from 29.6 to 32.3 min and from 12.6 to 14.3 min, respectively). The average infusion rate necessary to maintain approximately 95% twitch suppression was 1.35 μg/kg/min. Recovery indexes from infusions were 5–95% 33.2 ± 1.8 min and 25–75% 15.0 ± 0.6 min, not differing significantly from recovery indexes from single bolus doses. Twenty-five patients received neostigmine (0.06 mg/kg) with atropine (0.05 mg/kg) at twitch height recovery of between 6% and 21%. Antagonism to 95% control twitch height developed within 6.8 ± 0.3 min, and the neostigmine-accelerated 25–75% recovery index was 2.8 ± 0.2 min.

Conclusions: 51W89 is a potent nondepolarizing neuromuscular blocking agent that shows noncumulative intermediate-duration neuromuscular blocking pharmacodynamics. (Key words: Neuromuscular relaxants. 51W89: neuromuscular pharmacology. Nondepolarizing neuromuscular blocking agents.)

NEUROMUSCULAR blocking agents have been used widely in anesthesia for many years. None of the currently available drugs is ideal. In 1975, Savarese and Kitz1 publicized the deficiencies of available neuromuscular blocking agents and identified the need for novel short, intermediate, and long-acting nondepolarizing neuromuscular blockers that would be free of cardiovascular side effects and that would not show cumulative effects. Toward this end, we have seen the development of atracurium, vecuronium, rocuronium, mivacurium, doxacurium, and pipercuronium. One of the ten stereoisomers of atracurium is 51W89, chemically designated as [(1R, 1'R, 2R, 2'R)-2',(3,11-dioxo-1,10-dioxatridecamethylene) bis (1, 2, 3, 4-tetrahydro-6, 7-dimethoxy-2-methyl-1-veratrylisoquinolinium)] dibenzenesulfonate] (fig. 1). 51W89 is a potentially advantageous nondepolarizing neuromuscular blocking agent because preclinical pharmacologic studies in cats,2,3 dogs, and Rhesus monkeys1 have shown that it is more potent than atracurium but has similar neuromuscular blocking effects in terms of onset, duration, and recovery times. More importantly, when the cardiovascular effects of 51W89 were studied...
in monkeys, dogs, and cats, doses many times greater than the ED₅₀ for neuromuscular blockade had minimal effects on blood pressure or heart rate in these species. The same studies in cats, dogs, and monkeys also suggested that 51W89, in contrast to atracurium, is devoid of histamine-releasing properties.

On the basis of its preclinical pharmacologic advantages, 51W89 appears to have potential clinical advantages over currently available intermediate-acting nondepolarizing relaxants. This investigation of the safety and efficacy of 51W89 therefore was performed in human subjects to establish its neuromuscular blocking potency and pharmacodynamic profile. A lack of cumulative neuromuscular blocking effects already noted in animals, defined as a lack of relationship of rate of recovery from neuromuscular blockade to size of dose or duration of administration by infusion, also was to be evaluated in the current study in human subjects.

Methods

Patient Preparation and Monitoring

The study was approved by the Institutional Review Board of The New York Hospital. All patients gave written informed consent for all monitoring, data collection, and anesthetic procedures. Ninety-nine patients, ASA physical status 1 or 2, undergoing low- to moderate-risk surgery were studied. Female patients of childbearing potential were excluded from the first part of this study. Thereafter, women eligible for enrollment were required to be nonpregnant and not lactating. Any patients with a history of neuromuscular, cardiovascular, pulmonary, renal, hepatic, or neurologic disorders were excluded. The mean patient ages and weights ± SE were 39.3 ± 0.9 yr and 77.4 ± 1.3 kg, respectively.

On the day of the study, 20-G intravenous catheters were inserted, and midazolam (4–6 mg) was administered intravenously for sedation. Anesthesia was induced with thiopental (4–10 mg/kg) and fentanyl (2–9 mg/kg) intravenously in divided doses. Oxygen was delivered by face mask. The trachea was intubated without a relaxant, occasionally using lidocaine (4%) spray as a topical anesthetic. Ventilation was controlled throughout the study to maintain end-tidal carbon dioxide tension between 28 and 35 mmHg. Esophageal temperature was monitored and maintained between 35.5°C and 37.5°C by the use of warmed intravenous fluids and warming blankets. A 16-G intravenous catheter was inserted in the contralateral arm for blood sampling after the induction of anesthesia.

Anesthesia was maintained with nitrous oxide and oxygen (70:30), and additional doses of thiopental, fentanyl, and midazolam were given intravenously as needed to maintain a stable depth of anesthesia. The electrocardiogram was monitored continuously (Marquette model 700 or 710). Arterial pressure was measured by oscillometry (Dinamap), tonometry (N-CAT) or directly via a 20-G radial arterial cannula through a transducer. Heart rate was measured by oscillometry or, for the patients with arterial catheters, continuously by a Grass 7P44 tachograph triggered by the arterial pulse waveform. Hemodynamic data are presented in detail in a manuscript in press.

The mechanomyogram of thumb adduction was quantitated with a Grass FT10 force-displacement transducer. The supramaximal single twitch of the thumb was evoked at 0.15 Hz using square-wave pulses 0.2 ms in duration, generated by a Grass S88 stimulator and applied through a stimulus isolation unit to the ulnar nerve at the wrist via 23-G steel needle electrodes placed subcutaneously approximately 5 cm apart. Train-of-four stimulation (2 Hz for 2 s) was applied every 10 s during recovery from neuromuscular blockade.

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

Muscle Relaxant Administration and Pharmacodynamics

After a 3-min stable baseline period, 51W89 was injected rapidly (5–10 s) into a rapidly flowing intravenous fluid stream. Measurements of maximal twitch depression as well as arterial pressure and heart rate changes were obtained before any patient stimulation.
Fig. 2. A recording of the response of a single patient to neuromuscular stimulation at a frequency of 0.15 Hz. This patient received 51W89 in two doses, as described in Results. The initial dose was given at the first mark on the time chart. The second dose was given 8 min later, as indicated by the second mark, at the point of maximal response to the initial dose of relaxant.

(surgery) was begun. In the first part of the study, a group of 39 patients received an initial 51W89 dose administered in divided doses totaling 0.15 mg/kg. One subgroup of three patients and four subgroups of nine patients received first dose portions of approximately ED₁₀, ED₂₅, ED₅₀, ED₇₅, or ED₉₅. The first subgroup was administered a first dose portion of 0.04 mg/kg, which was estimated to be an ED₂₅ dose based on preclinical studies in which 51W89 was about 30–50% more potent than atracurium. Log probit analysis of the accumulated dose-response data was used to determine the first dose portion for each subsequent subgroup. After maximal twitch suppression following the first dose portion was obtained, the second dose portion was administered, to bring the total initial dose to 0.15 mg/kg (fig. 2). In the second part of the study, separate patients received 2, 4, or 8 × ED₉₅ boluses of 51W89 based on the results of the dose-response portion of the study. A control group received a 2 × ED₉₅ bolus of atracurium (0.5 mg/kg) for comparison with 51W89. Recovery from neuromuscular block induced by the second dose portion of 51W89 was observed to at least 25% of control twitch height before an additional bolus of 0.025 mg/kg was given or a continuous infusion begun to maintain clinical relaxation.

Infusion of 51W89

The initial rate of infusion of 51W89 was 5 μg/kg/min for the first 39 patients and 3 μg/kg/min for subsequent patients receiving infusions. Neuromuscular block was maintained within the ranges of 90–99% by adjusting the infusion rate every 3 min until stable block was achieved. Recovery was allowed to proceed spontaneously in the odd-numbered patients at the end of surgery, or a single intravenous injection of 0.06 mg/kg neostigmine and 0.03 mg/kg atropine was administered to the even-numbered patients when the twitch response had recovered spontaneously to approximately 10% of the baseline value after the initial dose, at the termination of infusion, or after the last maintenance bolus dose. The rate of spontaneous recovery from neuromuscular blockade was measured and compared among the various dose groups and with the atracurium group. Spontaneous recovery from single bolus doses and infusions was compared with pharmacologically accelerated recovery. Recovery intervals from 5% to 95% and from 25% to 75% twitch heights after the initial bolus dose and after termination of infusions of 51W89 were compared to ascertain whether a cumulative pharmacodynamic effect was evident.

Statistical Analysis

Data were analyzed using SAS software, version 6.07. Where confidence intervals were applied, an α level of 0.05 was used to define statistical significance. All data are presented as mean ± SE.

Results

Mechanism of Block

Fade of train-of-four responses and facile antagonism by neostigmine (see below) were noted consistently at many levels of neuromuscular block. These observations are compatible with a nondepolarizing mechanism of block.

Dose-Response and Duration

Dose-response data are summarized in tables 1 and 2. The dose-response relationships were constructed.

<table>
<thead>
<tr>
<th>Table 1. Patient Response to Initial Dose of Muscle Relaxant</th>
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<tbody>
<tr>
<td><strong>Dose (mg/kg)</strong></td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>51W89</td>
</tr>
<tr>
<td>0.02</td>
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<tr>
<td>0.03</td>
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<tr>
<td>0.04</td>
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<tr>
<td>0.05</td>
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<tr>
<td>0.1</td>
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<tr>
<td>0.2</td>
</tr>
<tr>
<td>0.4</td>
</tr>
<tr>
<td>Atracurium</td>
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<tr>
<td>Values are mean ± SE.</td>
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</tbody>
</table>

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from twitch suppression data obtained after the administration of the first portion of the initial doses of 51W89 in the first part of the study (fig. 2). Ordinary least-squares regression (linear regression) of the probit of maximum twitch suppression versus the common logarithm of the 51W89 dose was used to generate the dose-response line (fig. 3). All probit values were presented and analyzed on a scale of 2–8. If no block was observed, a probit value of 2 was assigned, and if complete block was observed, a probit value of 8 was assigned. The 51W89 ED₉₅ and ED₃₀ neuromuscular blocking doses were estimated from the regression equation. The calculated ED₉₅ for neuromuscular blockade was 0.048 mg/kg (95% confidence limits 0.03, 0.08). The calculated ED₃₀ was 0.029 mg/kg (95% confidence limits 0.02, 0.05).

Increasing dosage of 51W89 resulted in shorter mean times to onset of maximum neuromuscular block. Onset at 0.4 mg/kg (1.9 ± 0.1 min) was 3.3 min faster than at 0.10 mg/kg (5.2 ± 0.3 min).

After 0.1 mg/kg (a 2 × ED₃₀ dose), the mean duration from injection to recovery to 95% of control force of twitch was 64.4 ± 3.9 min. After 0.2 and 0.4 mg/kg (4 and 8 × ED₃₀, respectively), recovery to 95% of control occurred in 87.0 ± 4.3 and 121.0 ± 5.9 min, respectively.

The clinical duration, i.e., time from injection to return to twitch to 25% of control, varied from 45.0 ± 2.4 min after 0.1 mg/kg to 91.3 ± 3.3 min after 0.4 mg/kg (2 and 8 × ED₃₀, respectively).

Mean recovery intervals from 5% to 95% and from 25% to 75% twitch height ranged from 29.6 to 32.3 min and from 12.6 to 14.3 min, respectively, after bolus doses of 0.1–0.4 mg/kg. They did not differ statistically. When plotted graphically, they appear as parallel recovery patterns (fig. 4). The mean recovery intervals for all subjects at all single bolus doses combined were 31.1 (n = 23) and 13.5 min (n = 24) for 5–95% and 25–75%, respectively.

The T₄/T₁ ratio reached ≥70% within 2.3–5.3 min after the first twitch of the train-of-four had returned to 95% of control after bolus doses and within 3.5 min after infusions of 51W89.

**Continuous Infusion**

The average infusion rate necessary to maintain approximately 95% twitch suppression was 1.4 μg/kg/min (n = 27) for 51W89 (fig. 5) and 5.6 μg/kg/min (n = 9) for atracurium.

Spontaneous recovery from continuous infusion of 51W89 occurred at rates similar to those observed after single bolus doses. (table 2) Thirty-eight patients received infusions ranging in duration from 11 to 249 min (mean 109.2 min). Eighteen infusions lasted 2 h or longer. Mean 5–95% and 25–75% recovery indexes during spontaneous recovery from these infusions were

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**Table 2. Pharmacodynamics of Spontaneous Recovery**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>× ED₃₀</th>
<th>Time to 25% Recovery (min)</th>
<th>Time to 95% Recovery (min)</th>
<th>Time to T₄/T₁ ≥ 0.7 (min)</th>
<th>Recovery Indices (min)</th>
</tr>
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<tbody>
<tr>
<td>51W89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>2</td>
<td>45.0 ± 2.4 (14)</td>
<td>64.4 ± 3.85 (9)</td>
<td>66.7 ± 4.9 (8)</td>
<td>12.6 ± 0.6 (10)</td>
</tr>
<tr>
<td>0.2</td>
<td>4</td>
<td>68.3 ± 2.4 (15)</td>
<td>87.0 ± 4.3 (10)</td>
<td>89.9 ± 3.4 (10)</td>
<td>14.2 ± 1.2 (10)</td>
</tr>
<tr>
<td>0.4</td>
<td>8</td>
<td>91.3 ± 3.3 (13)</td>
<td>121.0 ± 5.9 (4)</td>
<td>126.3 ± 4.8 (4)</td>
<td>14.3 ± 1.7 (4)</td>
</tr>
<tr>
<td>Infusions</td>
<td>Atracurium</td>
<td>2</td>
<td>46.4 ± 1.6 (13)</td>
<td></td>
<td>15.0 ± 0.6 (19)</td>
</tr>
</tbody>
</table>

Values are mean ± SE (with n in parentheses).

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33.2 ± 1.8 (n = 8) and 15.0 ± 0.6 min (n = 19), respectively. These data were compared with recovery indexes from all single bolus doses and were not statistically different. The data show that recovery is independent of dose or duration of infusion at the dosages studied and over the range of infusions reported in this study (fig. 6).

Antagonism with Neostigmine
Twenty-five patients received neostigmine (0.06 mg/kg) with atropine (0.03 mg/kg) at between 6% and 21% (mean 12.6 ± 0.7%) twitch height during recovery from the initial dose or after discontinuation of the infusion. Antagonism to 95% of control twitch force developed within 6.8 ± 0.3 min (3.9–10.8 min). The neostigmine-accelerated 25–75% recovery index was 2.8 ± 0.2 min.

Discussion
This study has shown 51W89 to be a potent nondepolarizing neuromuscular blocking agent. When the ED₉₅ of atracurium is expressed in terms of its cation, rather than the besylate salt, 51W89 is approximately 3 times more potent as a neuromuscular blocking agent than atracurium. At doses up to the ED₉₅ (0.02–0.05 mg/kg), the onset of 51W89 (7 min) is slower than atracurium (3–4 min) and faster than doxacurium (10 min). This observation is consistent with their relative potencies because the more potent nondepolarizing neuromuscular blockers seem to have a slower onset.

Six isomers of atracurium, including 51W89, were tested by Wastila and Macheh in cats and were found to have varying potencies. The onset time to maximum block varied inversely with potency, although all isomers have the same chemical composition and molecular weight and differ only in terms of stereochemistry.

The 51W89 isomer is more potent than atracurium in humans, thus a somewhat slower onset would be anticipated. Onset of action for larger doses of 51W89 is

Fig. 6. Spontaneous recovery indexes of 25–75% for individual patients receiving infusions of 51W89 as a function of the duration of infusion of 51W89. There is no relationship to the 25–75% recovery index, which was 15 ± 0.6 (mean ± SE), and duration of 51W89 infusion.
dose-related. For example, by increasing the dose from 0.1 to 0.2 to 0.4 mg/kg (from 2 to 4 to 8 × ED₉₅), onset to maximum block was shortened from 5.2 to 2.7 and 1.9 min, respectively. The time to and ease of intubation were not evaluated in the current study. It has been shown, however, that intubation can be accomplished in 89% of patients 2 min after a 2 × ED₉₅ dose of 51W89 (0.1 mg/kg).⁹ Equipotent doses of vecuronium produce slightly faster onset times of 3.8 and 2.8 min,¹⁰ and a 2 × ED₉₅ dose of rocuronium produces maximal block in 1.5 min when onset is measured by repetitive train-of-four stimulation.¹¹

The duration of action of 51W89 is similar to that reported for atracurium at equipotent doses⁶ and the clinical duration of a 2 × ED₉₅ dose (45.0 min) was the same as atracurium in this study and similar to reported values for vecuronium (36.3 min) and rocuronium (40 min).¹¹ This duration is more than twice as long as mivacurium¹² (19.7 min) and about half as long as pancuronium¹³ (115.8 min) and doxracuronium (82.9 min). The clinical duration of effect increased only 150% and 200% with a 4 × ED₉₅ dose (68.3 min) and an 8 × ED₉₅ dose (91.3 min), respectively. The total duration increased about 23 min with a doubling of dose (table 2), suggesting that 51W89 will have an elimination half-life of about 23 min, similar to atracurium. Additionally, the consistent pattern of recovery independent of size of bolus dose or length of infusion suggests that 51W89 displays noncumulative pharmacodynamics with recovery always occurring during the drug’s elimination phase.¹¹

51W89’s spontaneous 25–75% recovery index of approximately 14 min is comparable to the other intermediate-duration nondepolarizing neuromuscular blockers vecuronium, 14.3 min¹⁴; rocuronium, 16.7 min¹¹; and atracurium, 11.8 min.⁶

Antagonism of residual block was accomplished easily once some evidence of spontaneous recovery was detected by administration of neostigmine and atropine. The 25–75% recovery index decreased to 2.8 min. The speed of reversal was comparable to reversal of mivacurium- and atracurium-induced block at a similar depth, with T1 of the train-of-four response returning to 95% within 7 min after injection of neostigmine.

The intermediate duration of action and lack of cumulative neuromuscular blocking effects of 51W89, like atracurium, probably are due to its decomposition and metabolism by Hofmann elimination, which is independent of hepatic or renal function.

In summary, 51W89, one of the ten stereoisomers of atracurium, is a potent intermediate-duration nondepolarizing neuromuscular blocking agent. Its pharmacodynamics are similar to atracurium: Duration and recovery profile are essentially the same and are independent of dose. Neuromuscular block is easily maintained at a stable level by infusion at a constant rate and does not diminish over time. Rate of recovery is independent of the duration of administration by infusion. Recovery can be accelerated with an anticholinesterase agent if needed. These attributes and 51W89’s probable lack of dependence on renal or hepatic metabolism suggest that the new drug should be a positive addition to the anesthesiologist’s armamentarium of neuromuscular blocking drugs, especially if its cardiovascular effects are absent in humans as in the preclinical studies. Further studies of its pharmacokinetics, hemodynamic effects, and pharmacodynamics in special populations are warranted.

References


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