

## Preanesthetic Train-of-four Fade Predicts the Atracurium Requirement of Myasthenia Gravis Patients

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**Background:** The most sensitive diagnostic criterion of myasthenia gravis is a decrement in the muscular response to repetitive stimulation. The authors hypothesized that myasthenia gravis patients who show a train-of-four ratio (T4/T1) < 0.9 in the preanesthetic period will have increased sensitivity to nondepolarizing neuromuscular blocking agents compared with myasthenia gravis patients with preanesthetic T4/T1 ≥ 0.9.

**Methods:** After institutional review board approval was obtained, 20 electrophysiologically documented myasthenia gravis patients were studied. Current pyridostigmine therapy was continued until the morning of surgery. Before induction of anesthesia, neuromuscular transmission was recorded from the hypothenar muscles using electromyography with train-of-four stimulation of the ulnar nerve. According to the T4/T1 ratio, patients were assigned to the "normal" group (T4/T1 ≥ 0.9) or the "decrement" group (T4/T1 < 0.9). After induction of intravenous anesthesia, the effective dose to achieve a 95% neuromuscular blockade (ED<sub>95</sub>) for atracurium was assessed with a cumulative bolus technique. Postoperatively, pyridostigmine was titrated to obtain a T4/T1 > 0.75 and to treat residual myasthenic symptoms.

**Results:** In 14 patients, preanesthetic T4/T1 was ≥ 0.9 (normal), whereas 6 patients presented with T4/T1 < 0.9 (decrement). Decrement patients had a lower ED<sub>95</sub> of 0.07 ± 0.03 mg/kg atracurium (mean ± SD) compared with normal patients

with an ED<sub>95</sub> of 0.24 ± 0.11 mg/kg atracurium ( $P = 0.002$ ). All patients were extubated within 30 min after surgery. Postoperative pyridostigmine infusion did not differ significantly between groups.

**Conclusions:** The requirement for atracurium is significantly reduced in myasthenia gravis patients with a T4/T1 ratio < 0.9 before anesthesia. This study indicates that routine neuromuscular monitoring in myasthenia gravis patients should be extended into the preinduction period to identify patients who require less atracurium. (Key words: Neuromuscular monitoring; pyridostigmine.)

MYASTHENIA gravis is a chronic autoimmune disease characterized by progressive weakness and easy fatigability of voluntary skeletal muscles with repetitive use followed by partial recovery with rest. Antibodies targeting the nicotinic acetylcholine receptor decrease the number of functional acetylcholine receptors, which induces impaired neuromuscular transmission, inadequate muscle, and increased sensitivity to the neuromuscular blocking effect of nondepolarizing muscle relaxants.<sup>1</sup> The balance between active and lost acetylcholine receptors determines clinical symptoms of the patient and modulates the sensitivity to nondepolarizing neuromuscular blocking agents.<sup>2</sup> Because treatment with anticholinesterases improves the clinical status of myasthenia gravis patients and decreases sensitivity to nondepolarizing muscle relaxants,<sup>3</sup> neuromuscular function of individual myasthenia gravis patients is difficult to predict from standard clinical parameters.

The most sensitive diagnostic criterion of myasthenia gravis is the decrement in the muscular response to repetitive supramaximal stimulation of a peripheral nerve. Neuromuscular monitoring using train-of-four stimulation is an established technique to measure fading caused by nondepolarizing neuromuscular blocking agents. Because muscle weakness occurs in non-myasthenia gravis patients when the ratio of the height of the fourth to the first response (T4/T1) is < 0.9,<sup>4</sup> neuromuscular monitoring may give the opportunity to determine

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the current status of neuromuscular transmission in the individual myasthenia gravis patient. We hypothesized that myasthenia gravis patients with a preanesthetic T4/T1 ratio  $< 0.9$  have a higher sensitivity to nondepolarizing neuromuscular blocking agents compared with myasthenia gravis patients with T4/T1 ratio  $\geq 0.9$  before induction of anesthesia. This study investigates the atracurium requirements for a 95% neuromuscular blockade in myasthenia gravis patients with respect to their preanesthetic T4/T1 ratio.

## Materials and Methods

After institutional review board approval and written informed consent were obtained, 20 myasthenia gravis patients (9 men and 11 women) were included in the study. Fifteen patients were scheduled for thymectomy, and five for other elective surgery. Myasthenia gravis was confirmed by preoperative electrophysiologic testing (20% decrement of the electromyogram response after supramaximal stimulation of the nervus medianus and/or the nervus facialis) or an antibody titer against the nicotinic acetylcholine receptor  $> 1$  nm ( $\alpha$ -bungarotoxin binding assay). With the current therapy, 6 patients were free of myasthenia gravis symptoms, and 14 patients presented with slight weakness, especially of ocular muscles. Seventeen patients required current pyridostigmine therapy, nine of whom received azathioprine in addition and one of whom received pyridostigmine and cyclosporine.

The patients' current pyridostigmine medication was continued, including on the day of surgery. Premedication consisted of atropine 5  $\mu\text{g}/\text{kg}$  (range, 0–7  $\mu\text{g}/\text{kg}$ ), 0.5 mg/kg promethazine (range, 0–0.7 mg/kg), and 0.5 mg/kg meperidine (range, 0–0.7 mg/kg) intramuscularly 30 min preoperatively. After adequate analgesia was provided by fentanyl (2  $\mu\text{g}/\text{kg}$ ), neuromuscular transmission was measured by electromyography. The ulnar nerve of the immobilized forearm was stimulated, and evoked electromyograms were measured from the hypothenar muscles. Supramaximal stimuli and control electromyogram response (T0) were established. Neuromuscular transmission was measured using train-of-four stimuli every 20 s. The amplitude of the first twitch response (T1) of each train compared with control electromyogram response (T1/T0) and the T4/T1 were recorded automatically (Relaxograph; Datex, Helsinki, Finland). Twitch response (T1) was stabilized for 5 min at T1/T0 =  $100 \pm 5\%$ . Thereafter, four consecutive T4/T1

values were averaged to assign each patient to one of two groups: the normal group, patients with a T4/T1  $\geq 0.9$ ; or the decrement group, patients with a T4/T1  $< 0.9$ .

Anesthesia was induced with propofol (1.5 mg/kg) and maintained with propofol (5–10 mg  $\cdot$  kg $^{-1}$   $\cdot$  h $^{-1}$ ) and fentanyl (0–5  $\mu\text{g}$   $\cdot$  kg $^{-1}$   $\cdot$  h $^{-1}$ ) according to clinical signs of inadequate anesthesia. Atracurium was then administered in incremental doses (1–5 mg according to the individual response) to achieve a T1/T0  $< 5\%$  to obtain a cumulative dose—response curve for each patient within 10 min. The twitch response was observed after each dose until a maximum effect was obtained. When three consecutive twitch responses (T1/T0) were equal, the next dose was administered. When T1/T0 was  $< 5\%$ , the trachea was intubated and mechanical ventilation with nitrous oxide in oxygen (fraction of inspired oxygen = 0.3) was adjusted to maintain an end-tidal carbon dioxide tension of  $36 \pm 2$  mmHg.

To maintain neuromuscular blockade during surgery one fourth the initial total dose of atracurium that produced  $\sim 95\%$  blockade was given whenever T1/T0 recovered to 25% of baseline. Nasopharyngeal temperature was controlled and maintained at  $37.0 \pm 1.0^\circ\text{C}$  using heating blankets. Thirty minutes before the estimated end of surgery, atracurium administration was terminated and bolus administration of pyridostigmine was titrated to obtain T4/T1  $> 0.75$ . On recovery of neuromuscular function, pyridostigmine infusion started with 1/500 per hour of the daily oral dose. The pyridostigmine infusion rate was adapted to obtain a T4/T1 between 0.8 and 0.9. As part of the concept, an attempt was made to extubate all patients within the first 30 min after the end of surgery.

All patients were transferred to the intensive care unit with continuous neuromuscular monitoring for 24 h. On clinical recovery of swallowing and gastrointestinal function, the pyridostigmine infusion was stopped, and oral therapy was restarted 3 h later.

### Statistical Evaluation

Data are described by mean values, SD, and ranges. The effective dose to achieve a 95% neuromuscular blockade (ED<sub>95</sub>) was calculated from the cumulative dose—response curve for each patient. The individual cumulative ED<sub>95</sub> was calculated by extrapolation from the linear regression of the degree of blockade in logit scale and the respective cumulative dose of atracurium in log scale. All values of the groups were compared using Student *t* tests.

Regression analyses between age, weight, duration of

disease, current pyridostigmin dose, antibody titer against nicotinic acetylcholine receptors, ED<sub>95</sub> atracurium, Osserman's classification, and T4/T1 ratio < 0.9 (yes/no) accordingly to the original dichotomous design were performed using linear least square regression analysis for each pair. Correlation coefficients of significant correlation are presented ( $P < 0.05$ ).

## Results

### Preanesthetic Values

During baseline measurements, mean T4/T1 ranged between 0.6 and 1.0 in all patients. In 14 patients (Osserman's class 1-3), T4/T1 was  $\geq 0.9$  (normal), whereas 6 patients (Osserman's class 1-3), presented with T4/T1 < 0.9 (decrement; fig. 1). Symptoms of myasthenia gravis had been reported by 12 of 14 patients in the normal group and by 2 of 6 patients in the decrement group. Groups differed significantly in age, weight, and duration of disease (table 1). Antibodies against the acetylcholine receptor were detected in 12 of 14 patients in the normal group and in 5 of 6 patients in the decrement group (decrement:  $24.2 \pm 22.3$  nm; normal:  $36.2 \pm 40.7$  nm; NS).

### Neuromuscular Blockade

Patients in the decrement group had a lower ED<sub>95</sub> and required less atracurium during surgery (table 2). Six of 14 patients in the normal group recovered spontaneously; in the other 14 patients, neuromuscular recovery

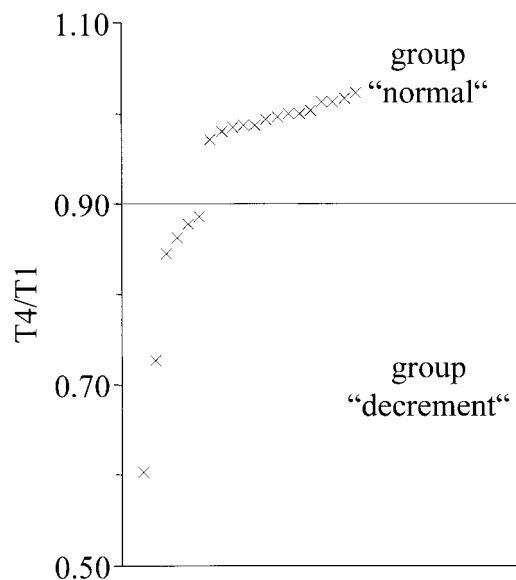


Fig. 1. Distribution of T4/T1 ratios (n = 20).

Table 1. Preanesthetic Parameters

	Normal	Decrement	P Value
Number		14	6
Age (yr)	50 ± 19	29 ± 4	0.017
Weight (kg)	82 ± 19	62 ± 21	0.047
Disease duration (month)	62 ± 34	8 ± 7	0.002
Current oral pyridostigmine (mg/day)	210 ± 140	300 ± 240	NS
Duration of surgery (min)	175 ± 50	155 ± 23	NS

Mean ± SD; n = 20.

NS = not significant.

was supported by pyridostigmine to achieve a T4/T1 > 0.75. The pyridostigmine dose to reverse neuromuscular blockade did not differ significantly between groups. Extubation was successful at the end of surgery in 19 of 20 cases. One patient required transient assisted ventilation for 30 min, although T4/T1 was > 0.75. Six patients complained of ocular weakness despite a T4/T1 > 0.8. These symptoms disappeared after the infusion rate of pyridostigmine was increased. Pyridostigmine infusion to treat residual myasthenic symptoms did not differ significantly between groups. Atracurium ED<sub>95</sub> and T4/T1 ratio < 0.9 (yes/no;  $r = -0.854$ ) as well as age and T4/T1 ratio < 0.9 (yes/no;  $r = -0.894$ ) were significantly correlated.

### Intensive Care Unit

On arrival at the intensive care unit, T4/T1 was  $0.88 \pm 0.15$  without differences between groups. Pyridostigmine infusion was terminated in 14 patients after 3-5 h. Only four patients required longer intravenous pyridostigmine infusion (maximum 22 h). All patients were switched to their oral medication within the first 24 h. Pyridostigmine requirement and duration of infusion did not differ significantly between groups.

## Discussion

The present study shows that myasthenic patients with a preanesthetic fading after train-of-four stimulation have a significantly decreased ED<sub>95</sub> of atracurium that is consistent with an increased sensitivity to nondepolarizing neuromuscular blocking agents in myasthenia gravis patients as described previously.<sup>3,5</sup> However, myasthenic patients without fading had a mean ED<sub>95</sub> value of 0.24 mg/kg atracurium, which is similar to the ED<sub>95</sub> of nonmyasthenic patients.<sup>6,7</sup> This wide variability in the

## PREDICTING ATRACURIUM REQUIREMENT IN MYASTHENIA GRAVIS

**Table 2. Neuromuscular Data and Medication Requirements during and after Anesthesia**

	Normal	Decrement	P Value
Neuromuscular blockade (intraoperative period)			
ED <sub>95</sub> atracurium (mg/kg)	0.24 ± 0.11	0.07 ± 0.03	0.002
Total atracurium (mg · kg <sup>-1</sup> · h <sup>-1</sup> )	0.18 ± 0.11	0.06 ± 0.04	0.032
Pyridostigmine to T4/T1 > 0.75 (mg)	2 ± 3	5 ± 4	NS
Postoperative period and ICU			
T4/T1 (arrival at ICU) (min)	0.91 ± 0.16	0.82 ± 0.09	NS
Pyridostigmine infusion rate (mg/h)	0.4 ± 0.4	0.4 ± 0.3	NS
Pyridostigmine infusion duration (h)	6.9 ± 7.8	5.8 ± 7.5	NS

Mean ± SD; n = 20.

ICU = intensive care unit; NS = not significant.

appropriate dose of nondepolarizing neuromuscular blocking agents in myasthenia gravis patients is well known<sup>8-12</sup> and stimulated investigations to identify determinants or predictors of the individual patient's sensitivity.

Clinical parameters, such as duration of disease or Osserman's classification, have been suggested to determine the individual response to neuromuscular blocking agents. However, these variables correlate poorly with the increased sensitivity.<sup>13,14</sup> As a consequence, the requirement of muscle relaxants is hard to predict from clinical parameters only. As an alternative, the pyridostigmine-free interval before administration of the muscle relaxant was suggested as a predictor. This is based on observations in myasthenia gravis patients showing a close relation between the pyridostigmine-free interval and the action of succinylcholine.<sup>15</sup> However, the predictive value of the pyridostigmine-free interval was not confirmed for nondepolarizing neuromuscular blocking agents in all studies.<sup>9,12,16</sup> During the present study, all patients received their last oral pyridostigmine within 1 h before baseline measurement, which could not prevent six patients from developing severe increased sensitivity to atracurium. A more molecular approach focuses on the autoimmune nature of myasthenia gravis. The titer of acetylcholine receptor antibodies correlates with the sensitivity to vecuronium.<sup>17</sup> However, this quantitative prediction depends on the existence of the antibody against the acetylcholine receptor, which is not given in all myasthenia gravis patients.<sup>18</sup> Monoclonal antibodies raised against purified nicotinic acetylcholine receptors can bind to each subunit. Although predominantly localized on the immunodominant  $\alpha$ -subunits, binding regions on the  $\beta$ -,  $\gamma$ - and  $\epsilon$ -subunits of human acetylcholine receptors have recently been identified in myasthenia gravis patients.<sup>19</sup> This may limit the predictive value of this approach. In the present study, anti-

body concentrations against the acetylcholine receptor were not related to the atracurium requirement. Together, these data show that clinical, pharmacologic, and immunologic approaches to predict the sensitivity to neuromuscular blocking agents are not adequate in every myasthenia gravis patient.

The present results suggest that the train-of-four ratio assessed immediately before induction of anesthesia can predict the atracurium requirements. This approach is based on the most sensitive diagnostic criterion of myasthenia gravis, the decrement in the muscular response to repetitive supramaximal stimulation of a peripheral nerve. Patients tolerate this procedure well because they are familiar with this stimulation because of the respective neurologic tests. We decided to discriminate between normal and decrement patients at a T4/T1 = 0.9, because this level represented an adequate recovery of neuromuscular function after a neuromuscular blockade in volunteers.<sup>4</sup> Extending the neuromuscular monitoring into the preanesthetic period allows for discrimination between well-compensated (n = 14) and borderline-compensated (n = 6) myasthenia gravis patients with immediate relevance to the required dose of the nondepolarizing neuromuscular blocking agent. With a T4/T1  $\geq$  0.9, large boli might be necessary. However, preanesthetic T4/T1 ratios < 0.9 indicate smallest atracurium doses ( $\approx$  2 mg).

Although the general recommendation to reduce the dose of nondepolarizing neuromuscular blocking agents<sup>3</sup> is not justified in myasthenia gravis patients with T4/T1  $\geq$  0.9, they showed wide ED<sub>95</sub> ranges for atracurium (0.17-0.48 mg/kg). Because of this individual variability in the response to muscle relaxants, accurate titration in combination with preoperative and intraoperative neuromuscular monitoring is essential for these patients, too.

Reversal of neuromuscular blockade in myasthenia gravis patients is controversial because it may be ineffective

during chronic pyridostigmine therapy.<sup>8,9,20</sup> Despite adequate muscle paralysis during surgery, all patients were successfully extubated not later than 30 min after the surgical procedure. This important clinical end point, however, was effectively supported by reversal of neuromuscular blockade with pyridostigmine in 14 patients.

Postoperative pyridostigmine infusion adjusted to maintain T4/T1 ratio at approximately 0.9 was effective to immediately treat bulbar or ocular weakness without any clinical signs of cholinergic crisis. In contrast to our expectation, the postoperative pyridostigmine requirements did not differ with respect to the preanesthetic evaluation of the decrement measured by train-of-four stimulation. This is consistent with the poor correlation between the preanesthetic fading and the current pyridostigmine medication. However, this observation does not challenge the predictive value of preanesthetic fading for the sensitivity to atracurium. Fading is a valuable indicator for the decreased number of functional nicotinic acetylcholine receptors at the time of induction of anesthesia and consecutively for the atracurium requirements at that time. However, pyridostigmine infusion rate is tapered to maintain adequate neuromuscular transmission over time and is consecutively more related to the severity of the disease.

In conclusion, the present data show that myasthenia gravis patients with a T4/T1  $\geq$  0.9 before induction of anesthesia require ED<sub>95</sub> of atracurium that is similar to the published values of nonmyasthenic patients. Patients with a T4/T1 < 0.9 require smallest doses of atracurium ( $\approx$ 2 mg). This suggests that neuromuscular monitoring using train-of-four stimulation should be extended into the preanesthetic period to predict the individual dose of atracurium necessary for neuromuscular blockade.

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