Neuromuscular effects of sevoflurane in myasthenia gravis patients

K. Nitahara*, Y. Sugi, K. Higa, S. Shono and T. Hamada

Department of Anesthesiology, Fukuoka University School of Medicine, Fukuoka, Japan

*Corresponding author: Department of Anesthesiology, Fukuoka University School of Medicine 7-45-1, Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. E-mail: nitahara@fukuoka-u.ac.jp

Background. Little information is available regarding the neuromuscular effects of sevoflurane in patients with myasthenia gravis (MG). We evaluated the neuromuscular effects of sevoflurane alone in patients with MG and in those with normal neuromuscular transmission.

Methods. Sixteen patients with generalized type MG (MG group) and 12 otherwise healthy patients (control group) entered into this study. Anaesthesia was induced with propofol, fentanyl, and midazolam followed by nitrous oxide in oxygen. Neuromuscular monitoring was recorded from the adductor pollicis muscle using electromyography with train-of-four stimulation of the ulnar nerve. After a stabilization period, and before sevoflurane administration, baseline T4/T1 was obtained and MG patients were classified as non-fade MG group (baseline T4/T1 < 0.90) (n = 10) and fade MG group (baseline T4/T1 < 0.90) (n = 6). End-tidal sevoflurane concentration was kept constant at 1.7% for 30 min and doubled thereafter to 3.4% and maintained for a further 30 min.

Results. Sevoflurane produced a concentration-dependent decrease in T1 and T4/T1 values. At 3.4% sevoflurane, T1 and T4/T1 decreased significantly from baseline values in all three groups. From baseline until the patient woke up from anaesthesia, the T4/T1 of the fade MG group was significantly lower than the other groups. At the end of anaesthesia, T4/T1 returned to values similar to the baseline in all three groups.

Conclusions. During sevoflurane anaesthesia, concentration-dependent inhibition of neuromuscular transmission was observed in MG and control patients. The inhibitory effects of sevoflurane were more prominent in MG patients with baseline T4/T1 < 0.90.

Br J Anaesth 2007; 98: 337–41

Keywords: anaesthetics volatile, sevoflurane; complications, myasthenia gravis; monitoring, neuromuscular function; neuromuscular transmission

Inhibitory effects of volatile inhalation anaesthetics on neuromuscular transmission have been shown in in vitro and in vivo animal studies. In human, volatile inhalation anaesthetics have also been reported to reinforce the effects of non-depolarizing neuromuscular blocking agents. The effect of volatile anaesthetics on neuromuscular transmission is a major concern in the anaesthetic management of patients with myasthenia gravis (MG), with or without the use of a neuromuscular blocking agent. The effects of halothane and isoflurane on neuromuscular transmission have been reported in patients with MG.

Sevoflurane has low blood/gas and tissue/gas solubility and may be a suitable volatile anaesthetic agent for general anaesthesia in patients with MG. However, little information is available regarding the neuromuscular effect of sevoflurane on MG patients. In this study, we investigated the effect of sevoflurane on neuromuscular transmission using electromyography (EMG) with train-of-four (TOF) stimulation in MG patients. We also investigated whether we could anticipate the degree of neuromuscular depressant effects of sevoflurane from the TOF ratio before administration. Indeed, the TOF ratio may reflect the fading of the response to four stimuli given every 0.5 s and the blockade of pre-junctional nicotinic acetylcholine receptors is thought to account for the fade that occurred during partial neuromuscular block.

Materials and methods

Sixteen MG patients (MG group) and 12 otherwise healthy patients of ASA physical status I–II, free from neuromuscular disease (control group), who were scheduled to undergo elective minor surgery or thymectomy, entered into this study. Institutionally approved, written informed consent was obtained from each patient. The diagnosis of MG patients was confirmed by characteristic
neurological findings, an anticholinesterase test, and electromyographic assessment. All MG patients were classified as having a generalized type of MG. Current anticholinesterase and steroid therapy were continued until the morning of surgery. Four of 10 patients in the non-fade group and 4 of the 6 patients in the fade MG group received pyridostigmine before operation. All patients in the non-fade MG group and five of the six patients in the fade MG group received prednisolone before operation. Anti-acetylcholine receptor antibodies were detected in 8 of the 10 non-fade MG patients and in 5 of 6 the fade MG patients.

On arrival into the operating theatre, monitoring of pulse oximetry, electrocardiography, and non-invasive arterial blood pressure was started. Anaesthesia was induced with propofol 2–2.5 mg kg\(^{-1}\), fentanyl 2–4 µg kg\(^{-1}\), and midazolam 0.04–0.08 mg kg\(^{-1}\), followed by nitrous oxide 60% in oxygen. The trachea was intubated without the use of a neuromuscular blocking agent. Patients were ventilated mechanically to keep the end-tidal carbon dioxide tension within 4.6–5.3 kPa. Tympanic temperature was maintained at 37.0 (1.0)\(^\circ\)C with a heating blanket.

Neuromuscular monitoring was recorded from the adductor pollicis muscle using EMG (Relaxograph\textsuperscript{TM}, Datex, Helsinki, Finland) with stimulation of the ulnar nerve of the immobilized forearm. The baseline calibration sequence was performed immediately after loss of consciousness. Supramaximal stimuli and control electromyographic responses were established. Neuromuscular transmission was measured using TOF stimuli every 20 s. The amplitude of the first twitch response (T1) of each train, compared with the control electromyographic response and the TOF ratio (T4/T1) was recorded automatically.

Baseline T1 and T4/T1 were obtained after a 15-min stabilization period. MG patients with T4/T1 ≥ 0.90 and T4/T1 < 0.90 were classified as the non-fade and fade MG groups, respectively. The end-tidal sevoflurane concentration was kept constant at 1.7% for 30 min and then doubled to 3.4% and maintained for a further 30 min. After 30 min of 3.4% sevoflurane, the concentration was adjusted during surgery at the discretion of the anaesthetist. The neuromuscular effects during the study were assessed at the end of a 15-min stabilization period (baseline), at the end of 1.7% sevoflurane, at the end of 3.4% sevoflurane, and when the patient woke up.

Hand skin temperature was monitored using a surface probe placed on the palm. Non-invasive blood pressure was monitored every 5 min, and when systolic blood pressure decreased to <80 mm Hg, ephedrine 4 mg i.v. was given. The trachea was extubated when the patient was fully awake and had an inspiratory force >25 cm H\(_2\)O and a vital capacity of at least 10 ml kg\(^{-1}\).

**Results**

No significant differences were noted among the groups with regard to age, height, weight, disease duration, or duration of surgery (Table 1). After 15-min stabilization, 6 of the 16 MG patients had baseline T4/T1 less than 0.9. Thus, 10 patients were classified as the non-fade MG group and 6 as the fade group. The mean T4/T1 at baseline was 0.99 (0.02) in the control group (n = 12), 0.97 (0.04) in the non-fade MG group (n = 10), and 0.81 (0.11) in the fade MG group (n = 6). No significant differences were noted between the non-fade and fade MG patients with regard to the daily doses of pyridostigmine and prednisolone (Table 1). There was no statistically significant difference with regard to antibody titres between the two MG groups [non-fade group 36.8 (51.5) nmol litre\(^{-1}\), range 1.5–162; fade group 277.4 (518.5) nmol litre\(^{-1}\), range 8.4–1200].

Hand skin temperature did not differ significantly between the three groups at any observation time. Hand skin temperature (mean of all patients) increased significantly after induction of anaesthesia from 32.5 to 34.8\(^\circ\)C; thereafter, it did not change until the end of surgery.

During sevoflurane anaesthesia, T4/T1 decreased in a concentration-dependent manner in all three groups (Table 2, Fig. 1). At 3.4% sevoflurane, T4/T1 decreased

<table>
<thead>
<tr>
<th>Table 1 Patient details. Values are presented as mean (sd), or number of patients. Data did not differ significantly between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n=12)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Disease duration (months)</td>
</tr>
<tr>
<td>Pyridostigmine (mg day(^{-1}))</td>
</tr>
<tr>
<td>Prednisolone (mg every 2 days)</td>
</tr>
</tbody>
</table>

Downloaded from https://academic.oup.com/bja/article-abstract/98/3/337/372627 by guest on 10 April 2019
significantly from baseline values to 0.70 (0.07) in the control group, 0.71 (0.19) in the non-fade MG group, and 0.43 (0.28) in the fade MG group, respectively (P<0.01). At the end of anaesthesia, T4/T1 returned to values not significantly different from baseline in all three groups. T4/T1 in the fade MG group was significantly lower than that in the other two groups at all observation points (P<0.01). The degree of T4/T1 depression from baseline was significantly greater in the fade MG group [22.7 (21.0)% at 1.7% and 48.5 (32.2)% at 3.4%] compared with control group [0.7 (1.6)% and 29.8 (6.9)%] and non-fade MG group [4.5 (5.7)% and 22.7 (12.7)%], P<0.01 at 1.7% sevoflurane, P<0.05 at 3.4% sevoflurane.

The mean T1 (% of control) at baseline was 94.8 (5.0) in the control group, 92.1 (10.8) in the non-fade MG group, and 92.0 (12.1) in the fade MG group. During sevoflurane anaesthesia, T1 also decreased in a concentration-dependent manner in all three groups (Table 3). At 3.4% sevoflurane, T1 decreased significantly from baseline to 75.7 (2.9) in the control group, 73.3 (11.8) in the non-fade MG group, and 52.7 (18.8) in the fade MG group (P<0.01). T1 in the fade MG group was significantly lower than that in the control group at 1.7% sevoflurane (P<0.05), and less than that in the other two groups at 3.4% sevoflurane (P<0.01).

Tracheal extubation was achieved at the end of surgery in all patients on reaching a maximum inspiratory force >25 cm H2O and a vital capacity of ≥10 ml kg⁻¹.

**Table 2** Change in TOF ratios. Values are presented as mean (sd). *P<0.01 compared with control and non-fade MG groups. †P<0.01 compared with baseline.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=12)</th>
<th>Non-fade MG group (n=10)</th>
<th>Fade MG group (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.99 (0.02)</td>
<td>0.97 (0.04)</td>
<td>0.81 (0.11)*</td>
</tr>
<tr>
<td>1.7% Sevoflurane</td>
<td>0.98 (0.02)</td>
<td>0.94 (0.07)</td>
<td>0.64 (0.22)*</td>
</tr>
<tr>
<td>3.4% Sevoflurane</td>
<td>0.70 (0.07)*</td>
<td>0.71 (0.19)*</td>
<td>0.43 (0.28)*</td>
</tr>
<tr>
<td>Awake</td>
<td>0.99 (0.01)</td>
<td>0.91 (0.12)</td>
<td>0.79 (0.17)*</td>
</tr>
</tbody>
</table>

**Discussion**

In our study, a concentration-dependent T4/T1 depression was observed in MG patients during sevoflurane anaesthesia. At 3.4% sevoflurane, which is approximately equal to 2 MAC (maximum admissible concentration) in 40-yr-old adults, T4/T1 decreased to 0.43 in the fade MG group and to 0.71 in the non-fade MG group. Nilsson and colleagues reported the effects of halothane on neuromuscular transmission in MG patients. In their study, after 15 min of 1.9 MAC halothane, T4/T1 of EMG responses in MG patients decreased to 0.72, which is similar to the value in non-fade MG patients at 3.4% sevoflurane in our study. Nilsson and Muller also studied the effects of isoflurane in MG patients and reported that after 15 min of 1.9 MAC isoflurane, T4/T1 of EMG responses in MG patients decreased to 0.59, which is in the middle of non-fade and fade MG values at 3.4% sevoflurane in our study. However, comparison between the above studies by Nilsson and colleagues and ours is difficult, as above studies did not differentiate between non-fade and fade MG patients and the duration of volatile anaesthetics administered and the choice of other anaesthetics are different.

Our study suggests that pre-anaesthetic T4/T1 values can predict the degree of depression of the neuromuscular transmission by sevoflurane during surgery in patients with MG. Neuromuscular function of individual MG patients is difficult to predict from standard clinical parameters such as baseline values, but pre-anaesthetic T4/T1 values provide a useful measure of the degree of depression that can be expected during surgery.

**Table 3** Changes in T1 (% of control). Values are presented as mean (sd). *P<0.05 compared with control group. †P<0.01 compared with control and non-fade MG groups. ‡P<0.01, ‡P<0.05 compared with baseline.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=12)</th>
<th>Non-fade MG group (n=10)</th>
<th>Fade MG group (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>94.8 (5.0)</td>
<td>92.1 (10.8)</td>
<td>92.0 (12.1)</td>
</tr>
<tr>
<td>1.7% Sevoflurane</td>
<td>92.3 (6.2)</td>
<td>87.2 (10.4)</td>
<td>78.8 (12.6)*</td>
</tr>
<tr>
<td>3.4% Sevoflurane</td>
<td>75.7 (2.9)*</td>
<td>73.3 (11.8)*</td>
<td>52.7 (18.8)*</td>
</tr>
<tr>
<td>Awake</td>
<td>91.1 (5.9)</td>
<td>82.6 (11.9)*</td>
<td>76.0 (14.5)</td>
</tr>
</tbody>
</table>
as duration of disease and Osserman’s classification (diagnosed by the presence of ocular muscle weakness and the degree of muscle weakness affecting muscles other than ocular ones). The maintenance dose of prednisolone and anticholinesterase or the titres of anti-acetylcholine receptor antibodies are not good predictors. No significant differences were noted between the non-fade and fade MG patients with regard to the daily doses of pyridostigmine and prednisolone, or in the antibody titres. However, monitoring of TOF ratio before administration of anaesthetics may give a valuable predictor for the neuromuscular function at the time of induction of anaesthesia. Reduced requirement of atracurium in MG patients with pre-anesthetic T4/T1 <0.9 has been reported during propofol and fentanyl anaesthesia\textsuperscript{12} and requirement for non-depolarizing neuromuscular blocking drugs is reduced with volatile inhalation anaesthetics compared with balanced anaesthesia.\textsuperscript{5} \textsuperscript{13} \textsuperscript{14} Sevoflurane has been shown to potentiate the effect of non-depolarizing neuromuscular blocking drugs more than the other volatile anaesthetics (e.g. halothane and isoflurane).\textsuperscript{14} \textsuperscript{15} Therefore, special attention is required during sevoflurane anaesthesia in cases where the non-depolarizing neuromuscular blocking drugs are necessary in MG patients, especially in patients whose preoperative T4/T1 is <0.9. Before sevoflurane administration, the fade in MG patients can be evaluated by monitoring the TOF ratios after the stabilization period with an i.v. agent such as propofol.

In our study, a significant decrease in T4/T1 at approximately 2 MAC sevoflurane was observed not only in MG patients but also in control patients. Caldwell and colleagues\textsuperscript{16} also reported that in volunteers; T4/T1 decreased significantly at 12% desflurane (i.e. at 1.67 MAC). In contrast, Nilsson and colleagues\textsuperscript{6} \textsuperscript{7} reported that 1.9 MAC of halothane and isoflurane had no inhibitory effects on T4/ T1 in control patients. Also, Fogdall and Miller\textsuperscript{17} reported that in patients with normal neuromuscular transmission receiving enflurane at 1.67 MAC, no fade was observed at a frequency of 50 Hz. In an animal study, Suzuki and colleagues\textsuperscript{3} compared the neuromuscular blocking effects of sevoflurane, isoflurane, and halothane in cats and showed that only sevoflurane, at 2 MAC, caused fade responses during 2 Hz stimulation. The site of action of volatile anaesthetics that produces inhibition of neuromuscular transmission is proposed to be both pre- and post-synaptic.\textsuperscript{18} \textsuperscript{19} However, drugs which act on acetylcholine receptors are thought to cause fade of muscle contraction responses during high-frequency stimulation by affecting mainly the pre-synaptic component.\textsuperscript{19} Our results suggest that sevoflurane may have a significant depressant action at pre-synaptic sites at neuromuscular junctions.

In our study, the concentration-dependent depression of T1 by sevoflurane was also observed. However, the drift in T1 in EMG responses has been reported after induction of general anaesthesia and is attributable to various mechanisms (e.g. change of muscle temperature and change of forearm position).\textsuperscript{20} \textsuperscript{21} As a result, at the end of anaesthesia, the T1 of EMG responses may only recover to 70–80% of control values in spite of TOF ratios >0.90, and this change varies greatly among individuals.\textsuperscript{21} In the present study, the T1 changes were within about 40% of control values in all groups. It is difficult to assess the changes of T1 induced by sevoflurane between and within groups with EMG, as we could not know how much drift is included in T1 changes. However, it is generally accepted that T4/T1 measured with EMG and those recorded with the mechanomyography (gold standard) provide similar information.\textsuperscript{22}

After discontinuation of sevoflurane, TOF ratios returned to values not significantly different from baseline in the three groups of patients. Tracheal extubation was achieved in all MG patients at the end of surgery with adequate ventilation. Low blood/gas and tissue/gas solubility might be partly responsible for this rapid recovery from neuromuscular depression by sevoflurane.

In conclusion, sevoflurane has an inhibitory effect on neuromuscular transmission in both MG and control patients. The inhibitory effects of sevoflurane were more prominent in MG patients with baseline T4/T1 <0.90 than in those with baseline T4/T1 ≥0.90 and in control patients.

Acknowledgement
This work was supported by grants from the Clinical Research Foundation, Fukuoka, Japan.

References
1 Kennedy R, Galindo A. Neuromuscular transmission in a mammalian preparation during exposure to enflurane. Anesthesiology 1975; 42: 432–42