J Anesth (1996) 10:157–162

Journal of
Anesthesia

Original articles

Neuromuscular effects of sevoflurane in patients with myasthenia gravis

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Abstract: The current study evaluated the neuromuscular responses following administration of sevoflurane in 14 patients with myasthenia gravis (MG) (I–IIb in Osserman's classification) scheduled for thymectomy and in 11 control patients (ASA I–II) who underwent elective surgery. The electromyographic (EMG) response of the abductor digiti minimi was measured following train-of-four (TOF) stimulation of the ulnar nerve every 20 s. After induction of anesthesia with a combination of 3–4 mg·kg^{-1} thiopental and 1–2 μg·kg^{-1} fentanyl with 66% N_2O and oxygen, an inspired concentration of 4% sevoflurane was administered via a face mask for 7 min. Anesthesia was maintained during surgery with 66% N_2O in oxygen and with 1 minimum alveolar concentration (MAC) of end-tidal concentration of sevoflurane. The T1 (the amplitude of the first response) values decreased more profoundly in the MG patients than in the control patients at the end of surgery ($P < 0.05$). Following administration of 4% sevoflurane for 7 min, the TOFR (the ratio of the fourth TOF to the first response) values revealed depressions greater than 10% of preinhalation values in 11 of 14 MG patients with a marked individual variation. This attenuated response was followed by a further depression of the TOFR values with increasing time of 1 MAC sevoflurane anesthesia. On the other hand, no notable changes were observed in patients with normal neuromuscular functions. The most significant factor that correlated with the depression of the TOFR values induced by 1 MAC sevoflurane was the anti-AchR antibody titers ($P = 0.029$). Our results indicate that MG patients have an increased neuromuscular sensitivity to sevoflurane.

Key words: Myasthenia gravis, Sevoflurane, Neuromuscular function, T1, TOFR

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Received for publication on November 27, 1995; accepted on February 7, 1996

Introduction

Autoimmune antibodies in myasthenia gravis (MG) can cause a curare-like effect at the neuromuscular junction [1–3]. This is followed by increased neuromuscular sensitivity to volatile anesthetics [4,5] as well as nondeporalizing muscle relaxants [6,7]. Sevoflurane is a particularly suitable induction agent because of its low blood-gas partition coefficient (0.63), pleasant odor, and decreased pungency [8]. A high concentration of the inspired sevoflurane is administered frequently via face mask during the induction of anesthesia. In addition, sevoflurane is known to enhance the effects of neuromuscular blocking agents [9–10]. Thus, even in the absence of neuromuscular blocking drugs, rapid administration of sevoflurane as well as sevoflurane anesthesia can potentially cause significant neuromuscular effects in patients with MG.

To examine the effects of administration of sevoflurane on the neuromuscular junction, a 4% inspired concentration of sevoflurane was initially administered via face mask in 14 patients with MG and 11 patients with normal neuromuscular transmission. Following administration for 7 min, the T1 values and the ratio of the fourth train-of-four (TOF) to the first response (TOFR) were compared between groups. Additional neuromuscular measurements were taken at a 1 minimum alveolar concentration (MAC) end-tidal concentration of sevoflurane during surgery. In addition, we evaluated preoperative clinical prognostic determinants that could affect the neuromuscular sensitivity to sevoflurane in MG patients.

Materials and methods

The protocol was approved by our local ethics committee. Informed consent was obtained from all patients. Fourteen patients undergoing elective extended

thymectomy for myasthenia gravis (I–IIb in Osserman's classification) [11] and 11 patients with normal neuromuscular transmission of ASA physical status I–II (control) (mean age 35.0 ± 3.4 years; 4 men and 7 women) were included in this study. The control patients required anesthesia for minor orthopedic, dental, or ophthalmic surgery. The diagnosis of MG was confirmed by a typical case history, characteristic neurologic findings, a positive Tensilon test and/or the presence of serum acetylcholine receptor antibodies (anti-AchR ab). Acetylcholine receptor antibodies were measured by a radioimmunoassay using [^{125}I] α-bungarotoxin labeled human leg muscle AchRs as an antigen. Anticholinergic medication was withdrawn 12 h preoperatively. None of the patients was on immunosuppressive therapy. Only one patient was given daily oral predonisolone (10 mg) instead of anticholinesterases. Two MG patients had previously received steroid therapy, and two other MG patients received hydrocortisone 200 mg iv 2 h before the operation. Only the grade IIb patients (three patients) had low respiratory function (%VC < 80%). The clinical severity of MG was determined using Osserman's classification [11]. Demographic details of the MG patients included in this study are shown in Table 1. None of the control patients had neuromuscular, hepatic, or renal diseases, nor received any drug known to affect the neuromuscular function.

Patients received no preanesthetic medication. On arrival in the operating room, ECG and noninvasive blood pressure monitors were attached. The left forearm and hand were immobilized and prepared for stimulation of the ulnar nerve at the wrist via surface electrodes. The evoked electromyogram (EMG) was recorded from the abductor digiti minimi utilizing a Datex NMT-100 Relaxograph (Datex, Helsinki, Finland). Anesthesia was induced with thiopental 3–4 mg·kg^{-1} and fentanyl 1–2 μg·kg^{-1} with 66% nitrous oxide in oxygen. After loss of consciousness, the electromyograph was calibrated to the control values (T1 and TOFR values) of the train-of-four pattern at 2 Hz for 2 s with a supramaximal stimulating current every 20 s. T1 and TOFR values were defined as amplitudes of the first response and the ratios of the fourth TOF to the first response, respectively.

After measurement of the baseline T1 and TOFR values, a 4% inspired concentration of sevoflurane was administered via a face mask for 7 min. The T1 and TOFR values of patients with both groups were recorded every 1 min for 7 min. A 22-gauge catheter was inserted into the dorsal pedis artery for direct determination of arterial blood pressure and for blood gas analysis in MG patients. Tracheal intubation was performed without aid of a muscle relaxant in both groups. Anesthesia was maintained with 66% nitrous oxide in oxygen and age-adjusted 1 MAC of end-tidal concentrations of sevoflurane during surgery. The age-adjusted 1 MAC of sevoflurane was obtained according to the equation of Katoh et al. [12]. The neuromuscular function was also determined at 1 MAC steady-state end-tidal concentration of sevoflurane (approximately 60 min following tracheal intubation), at the end of

Table 1. Demographic details of MG patients

Patient number	Age	Sex	Anti-AchR antibody[a] (nM/l)	Duration of disease (month)	Clinical severity (Osserman's classification)	Anticholinergic medication (mg/day)
1	45	f	33	35	IIa	Pyridostigmine 60
2	34	f	24	20	IIb	Pyridostigmine 180
3	58	m	25	68	IIa	Pyridostigmine 120
4	50	f	0.5	13	IIa	Pyridostigmine 60[b]
5	50	f	0	3	I	Pyridostigmine 60
6	37	f	5.0	150	IIb	Pyridostigmine 360[c]
7	41	f	24	16	I	Pyridostigmine 30 Ambenonium 30
8	28	f	13	179	I	Pyridostigmine 180 Ambenonium 30
9	62	m	28	12	IIa	Pyridostigmine 240[b]
10	15	f	38	62	IIb	Pyridostigmine 180[c] Distigmine 10
11	44	f	1.3	106	IIa	Pyridostigmine 60
12	64	m	12	32	IIa	Pyridostigmine 0[d]
13	69	f	6	12	IIa	Pyridostigmine 120
14	32	f	0	10	IIa	Pyridostigmine 120

MG, myasthenia gravis; AchR, acetylcholine receptor.
I, ocular; IIa, mild; IIb, moderately severe.
[a]Normal: <0.3; [b]previously received steriod therapy; [c]preoperatively received hydrocortisone 200 mg; [d]received daily oral predonine (10 mg·day^{-1}).

surgery, and at the end of anesthesia (40–50 min after discontinuation of sevoflurane administration). Postoperatively, MG patients remained intubated to facilitate ventilatory support. In control patients, the final neuromuscular function was recorded at the time of extubation (20–30 min following termination of anesthesia).

Throughout the study, ventilation was controlled manually and/or mechanically to maintain an end-tidal CO_2 concentration of 35–45 mmHg, and esophageal temperature was maintained between 36.0°C and 37.0°C with a surface warming device. The left arm was also covered with a surgical sheet to keep the arm warm. End-tidal CO_2, O_2, N_2O, and sevoflurane concentrations were measured continuously using a multiple gas analyzer (Capnomac Ultima, Datex).

The results are expressed as mean ± SEM. Two-way analysis of variance (ANOVA) for repeated measurements was used to test the significance of the T1 and TOFR values within and between groups, followed by Student's *t*-test. To assess the dependence of the clinical parameters of MG (anti-AchR-ab titers, total preoperative anticholinesterases dose, duration of disease, and clinical severity) on the response to the steady-state end-tidal concentration of 1 MAC sevoflurane, univariate and multivariate analyses were performed. When MG patients received ambenonium and/or distigmine in combination with pyridostigmine, the total preoperative anticholinesterases dose was calculated by the following equation based on the relative potency ratios between pyridostigmine and ambenonium or distigmine: (pyridostigmine dose + 6 × ambenonium dose + 2 × distigmine dose). A stepwise forward procedure was used to select the variables with the greatest prognostic value. $P < 0.05$ was considered to represent statistical significance (Macintosh, Statview 4.01, Abacus Concepts, Berkeley, CA, USA).

Results

The clinical data for the MG patients are shown in Table 1. Three MG patients had only ocular signs (I), 8 had mild generalized (IIa), and 3, moderately severe generalized disease (IIb). The MG patients had varying degrees of anti-AchR antibodies (range 0–38 nM/l). In addition, the duration of disease and the anticholinergic dose were highly variable (Table 1). Duration of surgery was significantly longer in MG patients (185 ± 35 min) than in control patients (116 ± 26 min) ($P < 0.05$).

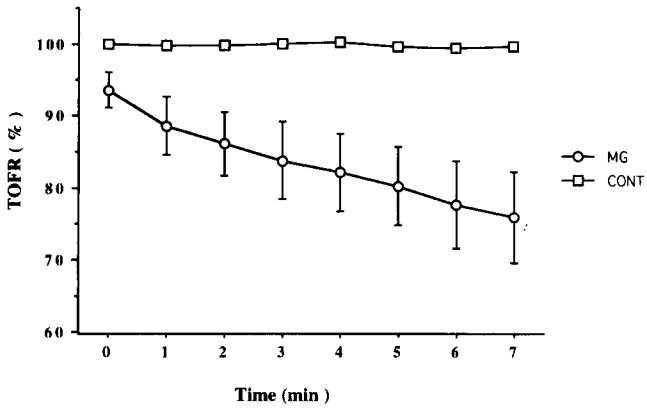

Fig. 1. Ratio of the fourth train-of-four (TOF) to the first response (*TOFR*) values in response to a 7-min administration of 4% sevoflurane via face mask. Each *point* indicates a mean value ± SEM. Myasthenia gravis (*MG*) patients ($n = 14$) experienced a time-dependent depression of TOFR values, while no notable changes were observed in the control patients ($n = 11$)

Following administration of 4% sevoflurane for 7 min, T1 values decreased to a similar degree in both groups. The significant differences between groups were observed at the end of surgery and at the end of anesthesia ($P < 0.05$) (Table 2).

Even prior to administration of 4% sevoflurane, six MG patients demonstrated TOF fade (defined as less than 95% of control) (Fig. 1). MG patients revealed a depression of the TOFR values in a time-dependent way ($P < 0.0001$) during the 7-min administration of 4% sevoflurane (Fig. 1). These effects were observed in 11 of 14 MG patients, i.e., a decrease of TOFR values of more than 10% of control values. Most notably in case 10, the TOFR values were decreased by a 90% depression of control values (Fig. 2). In addition, this depression observed in the majority of MG patients was

Table 2. T1 values at various time points during sevoflurane anesthesia

	Preinhalation period	7-min following 4% sevoflurane	1 MAC	End of surgery	End of anesthesia
MG ($n = 14$)	100	78.3 (4.0)	70.5 (4.6)	64.9* (4.2)	84.6* (2.3)
Control ($n = 11$)	100	81.3 (1.4)	78.6 (2.1)	77.9 (2.3)	94.5 (0.4)

MAC, minimum alveolar concentration.
Values are mean ± SEM (in parentheses). *$P < 0.05$.

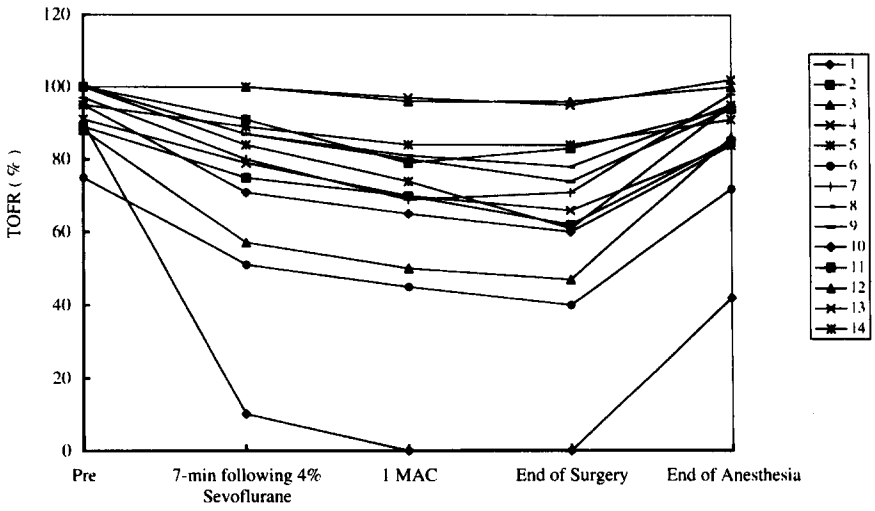

Fig. 2. Individual TOFR values from 14 MG patients at various time points during sevoflurane anesthesia. Numbers at the *right* correspond to the patient numbers from Table 1. *Pre*, prior to 4% sevoflurane administration; *7 min following 4% sevoflurane administration*, 7 min following 4% inspired concentration of sevoflurane by mask; *1 MAC*, during anesthesia with 1 MAC end-tidal concentration of sevoflurane; *End of surgery*, at the end of surgery (duration of surgery: 185 ± 35 min); *End of anesthesia*, at the end of anesthesia

Table 3. TOFR values at various time points during sevoflurane anesthesia

	Preinhalation period	7-min following 4% sevoflurane	1 MAC	End of surgery	End of anesthesia
MG (n = 14)	93.6 (2.5)	75.8 (6.3)	71.1 (6.0)	67.3 (6.1)	87.7 (4.1)
Control (n = 11)	100	99.6 (0.1)	99.5 (0.1)	99.6 (0.1)	100

TOFR, ratio of the fourth train-of-four (TOF) to the first response.
Values are mean ± SEM (in parentheses). MG patients showed significantly lower TOFR values than control patients at each time point ($P < 0.01$).

Table 4. Relationships between the TOFR values in response to 1 MAC sevoflurane and preoperative clinical values in MG patients

Variable	Probability value: Univariate analysis	Probability value: Multivariate analysis	Coefficient	SEM
Osserman's classification	0.045*	0.143	−13.92	8.63
Anti-AchR antibody titers (nM/l)	0.022*	0.111	−0.772	0.439
Total anticholinesterase dose[a] ($mg \cdot kg^{-1}$)	0.145	0.642	−0.034	0.071
Duration of disease (month)	0.364	0.560	−0.051	0.135

*$P < 0.05$.
[a] The total anticholinesterase dose was calculated based on the relative potency ratio between pyridostigmine and ambenonium or distigmine (see text).

followed by a further decrease of TOFR values with increasing time of 1 MAC sevoflurane anesthesia (Fig. 2). On the other hand, in control patients, the TOFR values did not change in response to either 4% sevoflurane administration for 7 min or to 1 MAC sevoflurane. Significant differences in the TOFR values between groups were observed at all time points ($P <$ 0.01) (Table 3).

By univarate analysis, anti-AchR antibody titers and clinical severity (Osserman's classification) correlated with the degree of sevoflurane-induced TOFR depression (measured at approximately 60 min following tracheal intubation). However, by multivariate analysis, none of the clinical parameters predicted the severity of TOFR attenuation induced by 1 MAC sevoflurane (Table 4). On the other hand, a stepwise forward procedure revealed that the most significant single factor that correlated with depression of TOFR values induced by 1 MAC of sevoflurane was the anti-AchR antibody titers ($P = 0.029$).

Discussion

No prior study has examined the neuromuscular effects of rapid administration of volatile anesthetics, probably because a relatively long duration of administration is necessary to achieve a steady-state condition at neuromuscular junctions. The present study demonstrated that a 7-min administration of 4% sevoflurane can impair neurotransmission in a majority of MG patients, as demonstrated by the depression of the TOFR values (Fig. 1). In addition, the sevoflurane-induced depression of TOFR values was enhanced with time during a steady-state end-tidal concentration of 1 MAC of sevoflurane anesthesia (Fig. 2, Table 3). This result suggests that the 7-min administration of 4% sevoflurane by mask did not reach the 1 MAC equilibrium condition in the neuromuscular junctions. Furthermore, sevoflurane anesthesia may enhance its neuromuscular effects with time similar to the time-dependent potentiation of nondeporalizing muscle relaxants by enflurane or desflurane [13].

Current volatile anesthetics all potentiate the effects of muscle relaxants. In the absence of neuromuscular drugs, however, neuromuscular depressant effects by volatile anesthetics in normal neuromuscular junctions can be detected only when isoflurane [14], enflurane [15], and desflurane [16] end-tidal concentrations exceed 1 MAC and when a stimulation rate greater than 120 Hz is used [17]. In addition, when measuring EMG response after a relatively short stabilizing period of the apparatus, it is common for the magnitude of the baseline T1 response to drift downward following administration of volatile anesthetics through unknown mechanisms [4,5]. On the other hand, the mechanomyographic (MMG) response increases [4,5]. Thus, it is likely that the EMG depression of T1 values observed in both groups did not necessarily reflect the accurate neuromuscular functions. However, the downward drift in EMG twitch response should have no effects on the accuracy of the TOFR determinations [18]. The present study revealed that even in the absence of muscle relaxants, the 7-min administration of 4% sevoflurane as well as 1 MAC sevoflurane anesthesia produced a marked depression of the TOFR values in the majority of MG patients (11/14) but not in control patients (Table 3). In other words, it was only in MG patients that a depression of the TOFR values accompanied the depression of the T1 values following sevoflurane. These findings are consistent with previous reports by Nilsson et al. on halothane or isoflurane in MG patients [4,5]. In addition, a significant difference in the T1 values between groups was found at the end of surgery (Table 2). This result also supports the significant neuromuscular effects of sevoflurane in MG patients.

Antibodies against acetylcholine receptors (AchRs) are specific for MG and detectable in more than 80% of MG patients [1–3]. However, anti-AchRs antibodies do not act primarily as simple competitive AchR antagonists, but rather through slower, more indirect mechanisms of AchR loss and morphologic disruption of the postsynaptic membrane [1–3]. Thus, antibody titers do not always correlate well with clinical severity. In the present study, a stepwise forward procedure showed that anti-AchR antibody titers were the most important determinant for the depression of the TOFR values induced by 1 MAC sevoflurane anesthesia. This result suggests that the increased sensitivity to sevoflurane in MG patients was attributable to the reduction of the number of available AchRs at the neuromuscular junction and that anti-AchR antibody titers can be a predictor of sevoflurane-induced neuromuscular changes. In addition to anti-AchR antibody titers, Nilsson and Muller have shown that the occurrence of HLA-B8 can predict the neuromuscular depression produced by isoflurane [5]. However, by univariate analysis, the depression of the TOFR values correlated to both the anti-AchR antibody titers ($P = 0.022$) and the clinical severity ($P = 0.045$), but they were found to be independent factors by multivariate analysis ($P > 0.05$) (Table 4). This indicates that there are complex mechanisms of action of sevoflurane at the myasthenic neuromuscular junction and that from the clinical data it is relatively difficult to predict individual variations of the sensitivity to sevoflurane. In addition, even 40–50 min after stopping anesthesia, the neuromuscular function of MG patients did not return to the baseline values (Tables 2, 3). The reasons for this are unclear, but it is likely that the residual concentrations of sevoflurane [19] as well as preexisting block by autoimmune antibodies [1–3] could affect neuromuscular transmission unfavorably. Thus, in MG patients neuromuscular monitoring is indispensable to determine individual sensitivities to volatile anesthetic agents even after the discontinuation of anesthetics.

In conclusion, rapid administration of 4% sevoflurane as well as 1 MAC of sevoflurane can cause neuromuscular depressant effects in a majority of MG patients. The anti-AchR antibody titers can be, to some extent, a predictor of the sevoflurane-induced variability of neuromuscular transmission in MG patients.

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