# Clinical Reports

# Vecuronium dose requirement and pupillary response in a patient with olivopontocerebellar atrophy (OPCA)

Masataka Kuroda MD,
Haruhiko Fukura MD PhD,
Nobuhiro Saruki MD,
Daisuke Yoshikawa MD,
Toshihiro Morita MD,
Fumio Goto MD

**Purpose:** Olivopontocerebellar atrophy (OPCA), a variant of spinocerebellar degeneration (Shy-Drager syndrome), is a systemic degenerative disorder affecting the neurons of multiple nuclei. We investigated the sensitivity to vecuronium and the pupillary responses to various stresses in a patient with OPCA.

**Clinical features:** A 65-yr-old woman with a six-month history of OPCA underwent a left upper lobectomy for lung cancer under propofol-$N_2O$ anaesthesia. She had symptoms of dysarthria, bulbar palsy, cerebellar ataxia, Parkinsonism, myosis, pyramidal signs and muscular atrophy of the distal extremities. A cumulative dose-response curve for vecuronium was constructed, and pupillary changes in response to various noxious stimuli were evaluated with concomitant recording of the Spectral-Edge-Frequency 90% (SEF90; the frequency below which 90 percent of the EEG power is located). The dose-response curve for vecuronium and the estimated $ED_{50}$ value (the 50% blocking dose of vecuronium) in this patient with OPCA were almost identical with those of five ASA I-II patients (27 $\mu g \cdot kg^{-1}$ *vs* 31 $\mu g \cdot kg^{-1}$). The pupil size and the SEF90 did not change after tracheal intubation or surgical stimulation in this patient, while in the control subjects (n = 3), these measures increased in response to both stresses.

**Conclusions:** The absence of pupillary and SEF90 responses to noxious stimuli suggests a sensitivity to propofol and/or central autonomic dysfunction in patients with OPCA. Although the dose requirement of vecuronium in this patient was similar to that of the control patients, the effects of neuromuscular blockers may vary depending on the severity of muscle atrophy.

**Objectif :** L'atrophie olivo-ponto-cérébelleuse (AOPC), une variante de la dégénérescence spinocérébelleuse (syndrome de Shy et Drager), est une atteinte dégénérative généralisée qui affecte les neurones de multiples noyaux. Nous avons examiné la sensibilité au vécuronium et les réactions pupillaires à différentes stimulations chez une patiente souffrant d'AOPC.

**Aspects cliniques :** Une femme de 65 ans souffrant d'AOPC depuis six mois a subi une lobectomie supérieure gauche, pour traiter un cancer du poumon, sous anesthésie avec propofol-$N_2O$. Elle présentait les symptômes suivants : dysarthrie, paralysie bulbaire, ataxie cérébelleuse, parkinsonisme, miose, signes pyramidaux et atrophie musculaire des extrémités distales. Une courbe dose-réponse cumulative pour le vécuronium a été élaborée et les changements pupillaires, en réaction à différents stimuli désagréables, ont été évalués à partir d'un enregistrement concomitant de fréquence spectrale limite à 90 % (FSL90 ; la fréquence sous laquelle se situe 90 pour cent de l'activité de l'EEG). La courbe dose-réponse au vécuronium et la valeur présumée de la $ED_{50}$ (la dose de vécuronium provoquant un blocage de 50 %) ont été presque identiques chez cette patiente et chez cinq patients ASA I-II (27 $\mu g \cdot kg^{-1}$ *vs* 31 $\mu g \cdot kg^{-1}$). Le diamètre pupillaire et la FSL90 n'ont pas changé après l'intubation endotrachéale ou la stimulation chirurgicale chez cette patiente, tandis que chez les patients témoins (n = 3), les réactions aux deux stimulations présentaient des mesures plus élevées.

**Conclusion :** L'absence de réaction pupillaire et FSL90 à des stimuli douloureux indique une sensibilité au propofol et/ou un dérèglement central autonome chez les sujets souffrant d'AOPC. Bien que la dose efficace de vécuronium soit similaire chez cette patiente et chez les patients témoins, les effets des bloqueurs neuromusculaires peuvent varier selon la sévérité de l'atrophie musculaire.

From the Department of Anesthesiology and Reanimatology, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371, Japan.

*Address correspondence to*: Dr. T. Morita. Phone: 0272-20-7111 (8453); Fax: 0272-20-8473; E-mail: tmorita@news.sb.gunma-u.ac.jp

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OLIVOPONTOCEREBELLAR atrophy (OPCA) or degeneration (OPCD), a variant of spinocerebellar degeneration (Shy-Drager syndrome),[1-3] is gradual in onset, slowly progressive, and caused by a systemic degeneration, primarily affecting the neurons of the inferior olives, pontine, arcuate, and lateral reticular nuclei.[4,5] Patients with OPCA exhibit marked dysarthria, Parkinsonism-ataxia complex, neuro-ophthalmologic signs, a variable degree of autonomic dysfunction, and upper and lower motor neuron signs.[4,5] Degenerative lesions of the cerebellum, brain stem, and spinal cord result in alterations in the cardiovascular and hypnotic effects of anaesthetics as well as in physiologic stress responses.[6] This neuronal degeneration is likely to cause abnormal responses to neuromuscular blocking drugs.[7]

The present case report investigates the sensitivity to vecuronium, and pupillary and electroencephalograph responses to various stresses in a patient with lung cancer associated with OPCA during propofol anaesthesia. Pupillary changes provide a good measure of noxious stimulation during anaesthesia.[8-10]

## Case history

A 65 yr-old woman with a three-year history of depression (weight 46 kg, height 153 cm) had been diagnosed as having OPCA. Despite treatment with antipsychotic drugs 100 mg amantadine and 50 mg sulpiride per day, her symptoms progressed. She also received 2 mg nilvadipine per day for treatment of hypertension. Six months later, a left lung adenocarcinoma (S4 and S5) was detected. Left upper lobectomy was scheduled under general anaesthesia. She had symptoms of dysarthria, bulbar palsy, cerebellar ataxia, Parkinsonism, and pyramidal signs. Muscular atrophy was overt in the distal extremities; the thenar and hypothenar muscles in both hands were very thin, and grip strength was decreased in both hands. She was unable to stand or to sit without assistance. She had bilateral myosis with anisocoria (L > R), but her light reflex was prompt. However, no evidence of orthostatic hypotension or urinary disturbance was present. She had several autoimmune antibodies, including antinuclear antibodies, anticardiolipin antibodies and rheumatoid factor, but had no clinical signs of systemic lupus erythematosus, antiphospholipid syndrome, or rheumatoid arthritis. Antineuronal antibodies such as anti-Yo (anti-Purkinje cell antibody) and anti-Hu (type I anti-neuronal nucleoprotein antibody) were not present either in the serum or cerebrospinal fluid (CSF). The CSF showed an increased IgG level of 8.2 $mg \cdot dl^{-1}$ (normal 0.5-4 $mg \cdot dl^{-1}$). Other data, including the electromyogram, plasma electrolytes, routine biochemical data, coagulation-fibrinolysis tests and ECG were almost normal, with the exception of a haemoglobin concentration of 11.2 $g \cdot dl^{-1}$. Magnetic resonance imaging (MRI) of the brain revealed atrophy of the pons and cerebellum, as well as enlargement of the ventricles. No metastatic invasion was detected in the central nervous system. Spinal MRI was not available.

### *Anaesthesia*

The patient received 10 mg famotidine *iv* one hour before surgery for prophylaxis of aspiration pneumonitis. Prior to induction of anaesthesia, standard monitoring (ECG, NBP, pulse oximetry) as well as a neuromuscular monitor (Datex NMT-100 Relaxograph, Finland) and a two-channel (fronto-mastoidal) processed EEG-monitor (pEEG Drager, Germany) were attached. The pEEG monitor calculates, on-line, the spectral edge frequency (SEF) after digitizing and Fast Fourier Transformation of the front-mastoidal raw EEG (a sampling rate of 128 Hz and an epoch length of 2 s).[11] The baseline value of the Spectral-Edge-Frequency 90% (SEF90; the frequency below which 90% of the EEG power is located) were 27 Hz with impedances below 4000 ohms. Propofol was administered in 10 mg increments every 10 sec while breathing $O_2$ via a face mask. The patient became unconscious and unresponsive at a dose of 70 mg (1.5 $mg \cdot kg^{-1}$) propofol, at which time the SEF90 reached 13 Hz. Blood pressure (130/80 mm Hg) and heart rate (70 $beats \cdot min^{-1}$) were stable. A continuous infusion of propofol was started at a rate of 5 $mg \cdot kg^{-1} \cdot hr^{-1}$. A 22-gauge catheter was inserted into the right radial artery for continuous monitoring of blood pressure and for blood gas analysis. Compound action potentials of the left abductor digiti minimi muscle were recorded after train-of-four stimulation (2 Hz for 2 sec every 20 sec) via surface electrodes over the ulnar nerve at the wrist. A normal response was seen in the amplitude of the first response ($T_1$) and the ratio of the fourth to the first response (TOFR). Three minutes later, vecuronium was injected *iv* in 10 $\mu g \cdot kg^{-1}$ increments every three minutes to a 96% $T_1$ depression. In the control patients (see later), the dose-response study was started following a five to seven minute stabilization period. Dose-response curves were constructed by linear regression of the logarithm of the dose against a logit transformation of the depression of the $T_1$ responses, from which the effective dose of vecuronium for suppression of $T_1$ response to 50% of control ($ED_{50}$) was derived.[12] The dose-response curve and the estimated $ED_{50}$ value of our patient with OPCA (27 $\mu g \cdot kg^{-1}$) were almost identical to those of the control patients (31 $\mu g \cdot kg^{-1}$)(Figure 1).

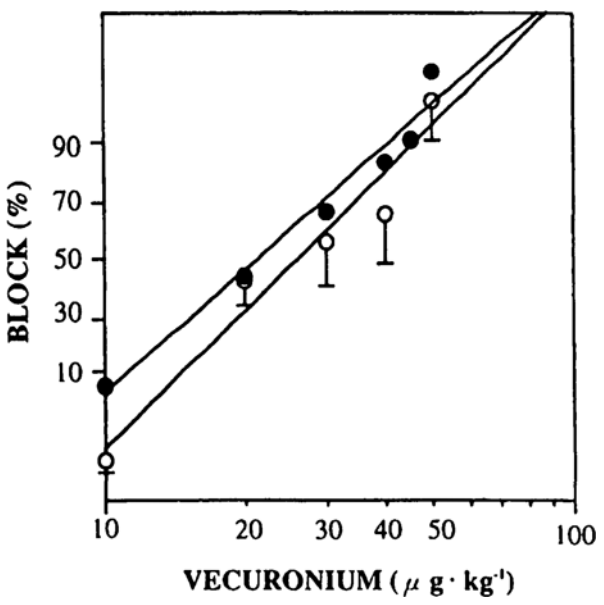


FIGURE 1 Dose-response curves for vecuronium in a patient with OPCA (●) and in the control patients (○) (n = 5) during propofol anaesthesia.

Tracheal intubation was performed using a 35 Fr BronchoCath (Mallinckrodt Medical, Inc., St. Louis, Mo) to facilitate one lung ventilation. Blood pressure and heart rate remained unchanged after tracheal intubation (BP: 140/90 mmHg; HR 72 beats·min$^{-1}$) or skin incision (BP: 150/92 mmHg; HR: 66 beats·min$^{-1}$). During surgery, anaesthesia was maintained using a continuous infusion of propofol (4-8 mg·kg·hr$^{-1}$) and vecuronium, in combination with 50-66% $N_2O$ in oxygen. The SEF90 and $T_1$ values were maintained in the ranges of 10-14 Hz and of 10-20% of control, respectively. Throughout surgery and anaesthesia, the patient's cardiovascular parameters were consistent with hyperdynamic circulation (BP: 140-160/80-100 mm Hg) without tachycardia (PR: 60-70 beats·min$^{-1}$). Thus, fentanyl 0.05 mg was given twice *iv* (during induction of anaesthesia and during surgery), and 1 mg nicardipine , occasionally. Surgery was uneventfully completed in four hours, and the infusions of propofol and vecuronium were stopped. At 30% recovery of $T_1$, edrophonium reversal was attempted in 200 μg·kg$^{-1}$ increments every three minutes: the first injection was preceded by atropine 0.25 mg. After complete recovery of neuromuscular function ($T_1$=96%, TOFR=93%), with a total edrophonium dose of 800 μg·kg$^{-1}$, and returning consciousness, the trachea was extubated. No respiratory disturbances developed. The total dose of propofol and vecuronium was 1460 mg at a mean infusion rate of 6.3 mg·kg$^{-1}$·hr$^{-1}$, and 8.64 mg at a mean infusion rate of 35 μg·kg$^{-1}$·hr$^{-1}$ during six hours of anaesthesia.

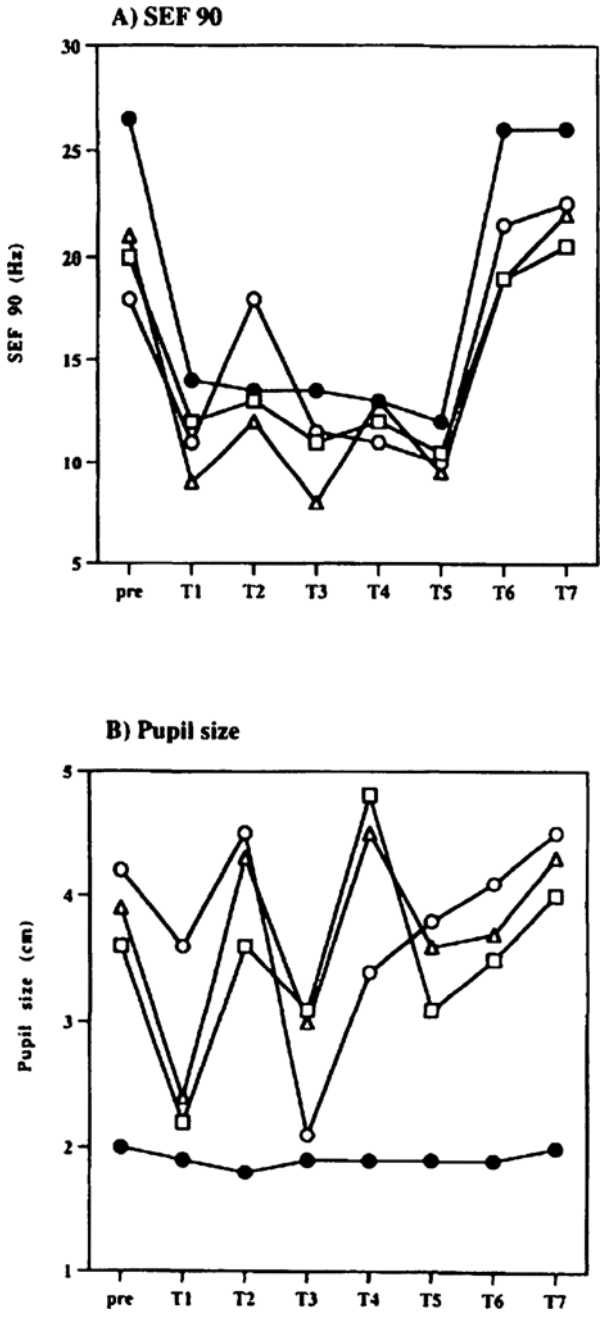


FIGURE 2 SEF 90 values (A) and pupil size (B) from a OPCA patient (●) and 3 control patients (□,○,△) at various time points. Pre: prior to induction of anaesthesia, T1: just before tracheal intubation, T2: just after tracheal intubation, T3: before skin incision, T4: just after skin incision, T5: 30 min after initiation of surgery, T6: just after tracheal extubation, T7: 10 min after tracheal extubation

*Control patients*

Following approval by the institutional ethics committee and written informed consent, five unpremedicated female ASA 1-II patients (mean age: 59.6 yr) requiring anaesthesia for minor surgery were assigned to the control group. Anaesthesia was induced with 2-2.5 $mg \cdot kg^{-1}$ propofol and 0.1 mg fentanyl, followed by a continuous infusion of propofol at 6-10 $mg \cdot kg^{-1} \cdot hr^{-1}$. Otherwise, anaesthetic technique and monitoring were the same as that used in the patient with OPCA; however, a standard single-lumen endotracheal tube was used for elective bronchoscopy. Because of technical difficulties in concurrent examinations, the data on pupil size and SEF90 were only obtained from three patients, but the data on neuromuscular function were obtained from all five patients.

*Pupil size and SEF90*

Left pupil size and SEF90 were measured prior to induction of anaesthesia, just before and after tracheal intubation, before and after skin incision, 30 min after the start of surgery, just after tracheal extubation, and 10 min after tracheal extubation. The right eye was kept covered. Each measurement took about 10 sec. Lighting was provided by laryngoscope bulbs. Photographs of the left pupil were taken using a digital still camera DSC-F (Cyber-Shot, SONY) from 10 cm above the left eye with a millimeter rule (100 mm) placed at the eyelid under controlled lighting conditions. The photographs obtained were then transferred into NIH image (Macintosh), in which the left pupil size was measured. In the control patients, the pupil dilated in response to tracheal intubation and surgical stimulation, which was associated with increases in the SEF90. By contrast, the pupil of the patient with OPCA was small in size compared with those of the control patients and did not show any change throughout the observation period. This patient's SEF only responded to the termination of propofol administration (Figures 2A, 2B).

In all patients, ventilation was controlled to maintain normocapnia and oesophageal temperature at 36-37°C. The left arm was covered with a surgical sheet to keep it warm.

## Discussion

This report demonstrates a patient with OPCA who had normal responses to vecuronium, but whose pupillary and SEF90 responses to tracheal intubation and surgical stimulation were absent.

Patients with Shy-Drager syndrome, a subtype of OPCA with a clinical predominance of autonomic failure, have been reported to develop severe hypotension during anaesthesia[1] and vocal cord paralysis at the post operative period.[2] There is insufficient information as to the most satisfactory anaesthetic technique in these patients. However, as these patients are likely to be highly sensitive to the anaesthetic agents,[1,2] deep anaesthesia may contribute to their hypotension. Furthermore, because of the presence of bulbar palsy, the residual actions of anaesthetics and neuromuscular blockers may increase the risk of postoperative aspiration and respiratory obstruction. Sleep apnoea has also been reported.[4] The fundamental principles of anaesthesia include maintaining an adequate depth of anaesthesia and neuromuscular blockade without causing hypotension, and eliminating the residual effects of anaesthetics and neuromuscular blockers after surgery. Thus, vecuronium which has an intermediate duration action with minimal cardiovascular effects was used as a muscle relaxant with great caution.[13] Propofol was chosen because of its possible antiparkinsonian effects[14] and favourable pharmacokinetic profile for rapid recovery after discontinuation.[15] Furthermore, propofol does not interfere with hypoxic pulmonary vasoconstriction, which is beneficial for oxygeneration during one-lung ventilation.[15] In addition to blood pressure and heart rate, the pupil size and SEF90 were used to monitor the depth of anaesthesia, to titrate the dose of propofol, and to evaluate physiologic stress responses.

Despite the fact that the patient with OPCA was given lower doses of propofol and fentanyl than the control patients, she did not exhibit haemodynamic, pupillary, or SEF90 responses at the time of tracheal intubation or skin incision. By contrast, the control patients showed increased pupil size and SEF90 in response to these noxious stimuli (Figure 2). One might propose that the anaesthetic depth was adequate to suppress autonomic responses to noxious stimuli in the patient with OPCA, but not in the control patients.[16] However, the OPCA patient's lack of haemodynamic responses is consistent with other reports of patients with Shy-Drager syndrome.[1,2] Based on the finding of the preexisting myosis, it is also likely that the absence of pupillary responses during anaesthesia seen in this patient is a feature of the disease, due to central autonomic dysfunction secondary to degeneration of the brain stem.[3-5] Monitoring of pupillary size was of little value in assessing the depth of propofol anaesthesia. Since changes in the pEEG are dependent on the anaesthetic agent used, the pEEG may also not be an ideal monitor of anaesthetic depth.[16] In addition, given the relatively high value of the baseline SEF90 (27Hz) observed in this patient, monitoring of SEF90 changes might be an unreliable guide to propofol dosage. The brain stem and the afferent system are known to regulate haemodynamic responses, pupillary

size, and corticocerebral function.[16] Thus, the lack of haemodynamic, pupillary and SEF90 responses suggest that degeneration of the brain stem and spinal cord enhanced the anaesthetic potency of propofol and fentanyl. Although propofol-$N_2O$ anaesthesia was successfully used in this patient with OPCA, she may have been given excessive doses of propofol, despite our efforts to provide adequate anaesthesia.

The dose-response curve for vecuronium and the estimated $ED_{50}$ value did not differ from those of control patients. In addition, edrophonium was successfully used to reverse the relatively deep vecuronium block ($T_1$=30%) at a reasonable dose (800 $\mu g \cdot kg^{-1}$).[17] These data indicate that this patient's sensitivity to nondepolarizing neuromuscular blockers was normal. However, muscle atrophy, a relatively common manifestation of this disease, is known to cause an increase in the numbers of muscle acetylcholine receptors.[7] This increase is usually associated with hyposensitivity to nondepolarizing neuromuscular drugs, and hypersensitivity to depolarizing neuromuscular drugs with development of hyperkalaemia.[7] In contrast, muscle weakness associated with muscle atrophy may itself result in neuromuscular blockade.[13] Thus, the balance between these two opposing effects may result in differing responses to neuromuscular blocking drugs among patients. Neuromuscular monitoring is indispensable to determine individual sensitivities to neuromuscular blocking drugs during anaesthesia in patients with OPCA.

A progressive cerebellar ataxia has been described in cancer patients, commonly those with lung cancer.[18–20] This disorder is called paraneoplastic cerebellar degeneration (PCD), and is caused by autoimmunity.[18–20] Although our OPCA patient had a variety of autoimmune antibodies, she did not exhibit specific antineuronal antibodies such as anti-Yo (anti-Purkinje cell antibody) or anti-Hu (type I antineuronal nuclear antibody). In addition, patients with PCD rarely develop Parkinsonism or myosis.[18–20] Thus, a diagnosis of OPCA rather than PCD was made by her primary physician.

Our experience suggests that patients with OPCA are sensitive to anaesthetics; however, there are few reliable clinical indicators for monitoring the depth of anaesthesia because of decreased autonomic responses to noxious stimuli. If muscle relaxants are needed, small, incremental doses of nondeporalizing neuromuscular drugs should be used.

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