Neuromuscular interaction of sevoflurane - cisatracurium in a myasthenic patient

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Purpose: To describe the influence of sevoflurane anesthesia on cisatracurium neuromuscular block in a myasthenic patient undergoing thymectomy.

Clinical features: A myasthenic patient (Osserman IIB) was managed for one year before surgery with 60 mg pyridostigmine qid, 50 mg immunaran tid and 30 mg prednisone therapy. Pyridostigmine was interrupted three months before surgery, and five sessions of plasmapheresis were done within 13 days before surgery. The neuromuscular response was monitored by Datex electromyographic response to train-of-four stimulation of the ulnar nerve. Sevoflurane 4% decreased the T_1/C ratio by 20%. Administration of $0.025 \text{ mg}\cdot\text{kg}^{-1}$ cisatracurium, during sevoflurane anesthesia, was followed by complete neuromuscular block for 45 min. Discontinuation of sevoflurane resulted, after 10 min, in recovery of the T_1 which reached T_1/C ratio of 50% after 30 min.

Conclusion: The marked sensitivity of this myasthenic patient to $0.5 \times \text{ED}_{95}$ of cisatracurium can be attributed to potentiation of cisatracurium neuromuscular block by sevoflurane, as evidenced by the reappearance of the first twitch of the train-of-four response 10 min after sevoflurane was discontinued.

Objectif : Décrire l'influence de l'anesthésie au sévoflurane sur le blocage neuromusculaire avec cisatracurium chez un patient myasthénique qui doit subir une thymectomie.

Éléments cliniques: Un patient myasthénique (Osserman IIB) a été traité pendant un an avant l'intervention chirurgicale avec 60 mg de pyridostigmine qid, 50 mg d'immunaran tid et 30 mg de prednisone die. La prise de pyridostigmine a été interrompue trois mois avant l'opération et cinq sessions de plasmaphérèse ont été réalisées pendant les 13 jours qui ont précédé l'opération. La réponse neuromusculaire a été suivie par la réponse électromyographique Datex à une stimulation en train-de-quatre du nerf cubital. Le sévoflurane à 4 % a fait baisser le ratio T_1/C de 20 %. L'administration de $0,025 \text{ mg}\cdot\text{kg}^{-1}$ de cisatracurium, pendant l'anesthésie au sévoflurane a été suivie d'un blocage neuromusculaire complet pendant 45 min. L'arrêt du sévoflurane a amené, après 10 min, la récupération de T_1 qui a atteint le ratio T_1/C de 50 % après 30 min.

Conclusion : La sensibilité marquée de ce patient myasthénique à la dose de $0,5 \times \text{ED}_{95}$ de cisatracurium peut être attribuée à la potentialisation, par le sévoflurane, du blocage neuromusculaire avec cisatracurium, comme l'a mis en évidence la réapparition de la première contraction de la réponse en train-de-quatre 10 min après l'arrêt du sévoflurane.

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IN a previous report we showed that, in a myasthenic patient undergoing thymectomy, the non-depolarizing muscle relaxant cisatracurium resulted in a more marked neuromuscular block than in normal patients.¹ This was attributed to the decreased "safety margin" of neuromuscular transmission in patients suffering from myasthenia gravis, with a subsequent increased sensitivity to non-depolarizing neuromuscular block.²⁻⁴

Previous reports have also shown that inhalational anesthetics such as halothane and isoflurane can depress neuromuscular transmission in myasthenic patients.⁵⁻⁶ Sevoflurane is an inhalation anesthetic with a low muscle-gas partition coefficient.⁷ No study has been published to demonstrate the neuromuscular effect of sevoflurane and its interaction with muscle relaxants in myasthenic patients.

The present report investigated the neuromuscular interaction of sevoflurane-cisatracurium in a myasthenic patient undergoing thymectomy.

Case report

A 42-yr-old, 70 kg woman, who had suffered from myasthenia gravis for one year, was scheduled for transsternal thymectomy. The main complaints were dysphagia, diplopia, generalized moderate muscle weakness, denoting Osserman IIB classification. Acetylcholine receptor antibodies were detected in the patient's plasma 86,00 nmol⁻¹L (normal value <0.4 nmol⁻¹L), and repetitive nerve stimulation revealed 53% decrement. Computed tomography scan revealed normal sized thymus. The patient was treated with 60 mg pyridostigmine qid, 50 mg immuran tid and 30 mg prednisone daily *po*. Pyridostigmine was stopped three months before surgery. The patient underwent within the 13 days before surgery, five sessions of plasmapheresis, that were followed by marked clinical improvement.

Neuromuscular transmission was monitored three minutes before induction of anesthesia by electromyography (EMG) using a Datex relaxograph monitor. The ulnar nerve was stimulated supramaximally at the wrist every 20 sec and the resulting EMG response of the adductor pollicis muscle was displayed. The monitor uses the train-of-four (TOF) principle at a stimulus frequency of 2Hz, and computes the ratio of the first twitch of TOF to the control twitch (T_1/C) ratio, as well as the ratio of the fourth twitch to the first twitch (T_4/T_1) ratio.

Anesthesia was induced and maintained by sevoflurane 4% in 3 L 50% N₂O:O₂. Five minutes after induction of anesthesia, the EMG monitor showed a 20% decrease of T_1/C ratio when 0.025 mg·kg⁻¹ cisatracuri-

FIGURE Electromyographic response to train-of-four stimulation of the ulnar nerve:

A. Sevoflurane 4% decreased T_1/C ratio to 0.8 after five minutes. Administration of 0.025 mg·kg⁻¹ cisatracurium, during continued sevoflurane anesthesia, resulted in complete neuromuscular block which lasted for 45 min.

B. Electromyographic tracing 10 min after discontinuation of sevoflurane. Recovery of the neuromuscular transmission reached T_1/C ratio of 0.5 after 30 min.

C. Administration of 0.05 mg·kg⁻¹ neostigmine at T_1/C ratio of 0.5 resulted in complete recovery, T_4/T_1 ratio of 1.0, after 10 min.

um (0.5 ED₉₅) was injected *iv*. The trachea was intubated with a 7.5 mm endotracheal tube. Administration of cisatracurium produced complete neuromuscular block in 120 sec, and no twitch response was recorded during the following 45 min (Figure A). Sevoflurane was then turned off, and 10 min later, T_1 appeared and reached T_1/C of 50% after 30 min (Figure B). A mixture of 0.05 mg·kg⁻¹ neostigmine and 0.02 mg·kg⁻¹ atropine was then administered, and was followed after 10 min by complete recovery of neuromuscular transmission, as evidenced by a T_4/T_1 ratio of 1.0 (Figure C).

Following recovery of neuromuscular transmission, N₂O was discontinued. The patient became conscious, resumed adequate spontaneous respiration and the trachea was extubated. The postoperative course showed a marked improvement in muscle power.

Discussion

Myasthenia gravis is an autoimmune disease⁸ resulting from the production of antibodies against the endplate acetylcholine receptors⁹ and, hence, the "safety margin"

of the neuromuscular transmission is decreased.^{2,3} Thus, myasthenic patients are sensitive to non depolarizing muscle relaxants,⁴ including cisatracurium.¹ Also, potent volatile anesthetics may impair neuromuscular transmission in the myasthenic patient.^{5,6} In our patient, administration of 0.025 mg·kg⁻¹ (= 0.5ED₉₅) cisatracurium following sevoflurane anesthesia, resulted in rapid and complete neuromuscular block which was maintained for 45 min. This contrasts with the normal clinical duration of cisatracurium neuromuscular block which is observed in non-myasthenic patients during barbiturate/nitrous oxide/opioid anesthesia, when the time to 25% twitch recovery ranges from 33-45 min after a single bolus of 0.1 mg·kg⁻¹ (= 2 x ED₉₅) cisatracurium,¹⁰ which is four times the dose used in our myasthenic patient.

The marked sensitivity of this myasthenic patient to a small dose of cisatracurium compared with normal patients or to our previously reported myasthenic patient¹ may be a normal variation response of the myasthenic patients to muscle relaxants, to the preoperative cessation of anticholinesterase therapy, or to potentiation of cisatracurium neuromuscular block by sevoflurane. The relatively rapid recovery of neuromuscular transmission following discontinuation of sevoflurane suggests that sevoflurane can markedly potentiate cisatracurium neuromuscular block in myasthenic patients.

Inhalational anesthetics may affect the neuromuscular transmission by presynaptic inhibition of acetylcholine mobilization and release, as well as by a decreased postsynaptic response;¹⁰⁻¹² the neuromuscular transmission is depressed in this order: sevoflurane, enflurane, isoflurane and halothane.¹¹ Volatile anesthetics can also potentiate the neuromuscular block of non-depolarizing muscle relaxants in a concentration-dependent manner, by acting mainly at the post junctional membrane.¹¹ A recent report has shown that sevoflurane produces time-dependent potentiation of vecuronium neuromuscular block.¹² Potentiation of nondepolarizing block by sevoflurane may be exaggerated in the myasthenic patients.

Potent volatile anesthetics such as sevoflurane and isoflurane not only potentiate non-depolarizing blockers in a dose dependent manner but also delay recovery of the neuromuscular transmission and impair neostigmine antagonism:^{1,3} discontinuation of the anesthetic will enhance recovery and improve reversal.¹³ However, elimination of volatile anesthetics is time-dependent. Thus, if the administration of isoflurane or sevoflurane is discontinued at the time of reversal, the impaired antagonism with neostigmine is reduced but not eliminated.¹³ In our patient, sevoflu-

rane was discontinued 30 min before reversal, when the T₁/C ratio reached 0.5. Subsequent reversal with neostigmine completely antagonized the residual neuromuscular block.

In conclusion, the present report shows a marked potentiation of neuromuscular block following the combination of sevoflurane and cisatracurium in a myasthenic patient. We recommend neuromuscular monitoring and titration of the dose of cisatracurium whenever it is administered during sevoflurane anesthesia, particularly in myasthenic patients. Also, the volatile anesthetic should be discontinued prior to reversal of neuromuscular block in order to enhance recovery of neuromuscular transmission.

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