Cisatracurium in a myasthenic patient undergoing thymectomy

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Purpose: The report investigates cisatracurium neuromuscular block in a myasthenic patient undergoing thymectomy.

Clinical Features: A myasthenic patient (Osserman II B) was prepared preoperatively with 240 mg·day^{-1} pyridostigmine. The neuromuscular block produced by 0.05 mg·kg^{-1} cisatracurium was monitored by Datex electromyography. The electromyographic response was compared with that in a control group of five non-myasthenic patients. In the myasthenic patient, cisatracurium resulted in a rapid onset of complete (97-98%) neuromuscular block, while a slow onset of partial (80-90%) block was achieved in the control group. Also, administration of 0.05 mg·kg^{-1} neostigmine at the end of surgery reversed the neuromuscular block of cisatracurium in the non-myasthenic patients, but did not change the rate of spontaneous recovery in the myasthenic patient.

Conclusion: The myasthenic patient is sensitive to cisatracurium, as evidenced by a more rapid onset and more marked neuromuscular block compared with the control non-myasthenic patients. This may be attributed to the decreased number of functional endplate acetylcholine receptors in the myasthenic patient, with a consequent decrease of the safety margin of neuromuscular transmission. Also, in contrast with the control group, the rate of recovery from neuromuscular block in the myasthenic patient was not enhanced by neostigmine at the end of surgery. This may be attributed to the prior inhibition of acetylcholinesterase by the preoperative pyridostigmine, as well as by possible desensitization of the cholinergic receptors secondary to prolonged pyridostigmine therapy.

Objectif : Étudier le blocage neuromusculaire produit par le cisatracurium chez un patient myasthénique subissant une thymectomie.

Éléments cliniques : Un patient myasthénique (Osserman II B) a été préparé à l'opération avec 240 mg·jour^{-1} de pyridostigmine. On a surveillé le blocage neuromusculaire produit par 0,05 mg·kg^{-1} de cisatracurium à l'aide de l'électromyographie Datex. La réponse électromyographique a été comparée à celle de cinq patients non myasthéniques d'un groupe témoin. Chez le patient myasthénique, le cisatracurium a provoqué un début d'action rapide du blocage neuromusculaire complet (97-98 %), tandis qu'un bloc partiel s'est lentement installé (80-90%) chez les patients témoins. De plus, l'administration de 0,05 mg·kg^{-1} de néostigmine à la fin de l'intervention a renversé le bloc chez les patients non myasthéniques, mais n'a pas changé la vitesse de la récupération spontanée chez le patient myasthénique.

Conclusion : Le patient myasthénique est sensible au cisatracurium comme l'ont mis en évidence la rapidité d'action et le blocage neuromusculaire plus marqué que chez les patients témoins. On peut expliquer cette situation par la baisse du nombre de récepteurs fonctionnels d'acétylcholine de la plaque motrice chez le patient myasthénique et par une baisse consécutive de la marge de sécurité de la transmission neuromusculaire. Par ailleurs, dans le groupe témoin, la vitesse de la récupération du blocage neuromusculaire n'est pas améliorée par la néostigmine administrée à la fin de l'opération. Ce qui pourrait relever de l'inhibition antérieure de l'acétylcholinestérase liée à l'administration préopératoire de pyridostigmine aussi bien qu'à la désensibilisation possible des récepteurs cholinergiques secondaire à la thérapie prolongée avec la pyridostigmine.

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MYASTHENIA gravis is an autoimmune disease[1] resulting from the production of antibodies against the endplate acetylcholine receptors[2] and, hence, the "safety margin" of the neuromuscular transmission is decreased.[3-4] Thus, myasthenic patients may be resistant to depolarizing muscle relaxants such as succinylcholine,[5] and sensitive to nondepolarizing muscle relaxants.[6] Atracurium is an intermediate-acting nondepolarizing relaxant, which undergoes organ-independent degradation in plasma by Hofmann elimination at physiological pH and temperature, as well as by nonspecific ester hydrolysis.[7] It has been used safely to induce neuromuscular blockade in myasthenic patients undergoing thymectomy.[8] Cisatracurium is a new nondepolarizing muscle relaxant which is a purified form of one of the 10 stereoisomeres that constitute atracurium.[9] Similar to atracurium, it undergoes spontaneous Hofmann elimination.[9] However, ester hydrolysis does not appear to play an important role in its degradation.[9] Also, in contrast with atracurium, it is not associated with histamine release in the clinical dose range.[9]

The present report investigates the neuromuscular block of cisatracurium and its reversal by neostigmine in a myasthenic patient undergoing thymectomy. The neuromuscular responses in the myasthenic patient were compared with those achieved in a control group of non-myasthenic patients undergoing elective surgery.

Methods

A 31-yr-old, 62 kg man who had suffered from myasthenia gravis for four months, was scheduled for transsternal thymectomy. The main complaints of the patient were diplopia, dysphagia, dysarthria and generalized moderate muscle weakness, denoting Osserman IIB classification. Prior to therapy, electromyography (EMG) revealed a 50% decrement with repetitive stimulation. Also, acetylcholine receptor antibodies were detected in the patient's plasma (20.96 $nmol \cdot l^{-1}$; normal 0.25-0.4 $nmol \cdot l^{-1}$). Computed Tomography scan revealed normal sized thymus. The patient was then treated for three weeks before thymectomy with 240 mg pyridostigmine daily, and for ten days prior to surgery with 40 mg prednisone daily, which resulted in a marked improvement of the muscle weakness and the clinical symptoms. Preoperatively, the patient received his usual morning dose (60 mg) of pyridostigmine. Premedication consisted of 5 mg diazepam *po* and 0.6 mg atropine *im*, one hour before surgery. Anesthesia was induced with 1.5 $mg \cdot kg^{-1}$ lidocaine, 2 $mg \cdot kg^{-1}$ propofol and 3 $\mu g \cdot kg^{-1}$ fentanyl. Neuromuscular transmission was monitored in the operating room by electromyography using a Datex Relaxograph monitor. The ulnar nerve was stimulated supramaximally at the wrist every 20 sec, and the resulting electromyographic response of the adductor pollicis muscle was displayed. The monitor uses train-of-four (TOF) stimulation at a frequency of 2Hz, and computes the ratio of the fourth to the first evoked response (T4/T1 ratio), as well as the ratio of the first twitch of the train-of-four to the control twitch (T1/C ratio). Following induction of anesthesia, and while the patient was breathing oxygen 100%, the electromyographic response was recorded. When a steady twitch response was achieved, 0.05 $mg \cdot kg^{-1}$ cisatracurium ($1 \times ED_{95}$) *iv* was injected. The time from the end of injection of cisatracurium until maximum neuromuscular block (onset time), as well as the degree of maximal block were recorded. The trachea was intubated at the time of maximal block, and anesthesia was maintained by $N_2O{:}O_2$ mixture (2:1), supplemented with an inspired isoflurane concentration of 1%. The time of recovery of the first twitch of the TOF to 25% of control value (recovery time) was monitored. Maintenance doses of 0.015 $mg \cdot kg^{-1}$ cisatracurium were administered at recovery of neuromuscular transmission to a T4/T1 ratio of 0.25. The time-intervals between the maintenance doses of cisatracurium were recorded. At the end of the procedure, which lasted for two hours, reversal of the residual neuromuscular block was attempted by the injection of a mixture of 0.05 $mg \cdot kg^{-1}$ neostigmine and 0.01 $mg \cdot kg^{-1}$ glycopyrrolate *iv*.

The same anesthesia technique was used in a control group of five non-myasthenic patients undergoing elective surgery (Table). Similar to the myasthenic patient, an initial dose of 0.05 $mg \cdot kg^{-1}$ cisatracurium was administered in the control group, and maintenance doses of 0.015 $mg \cdot kg^{-1}$ were administerted whenever T4/T1 ratio became 0.25. The onset time, the degree of maximal neuromuscular block, as well as the time intervals between the maintenance doses of cisatracurium, were monitored and compared with that achieved in the myasthenic patient. Also, the rate of recovery after the administration of the reversal mixture was monitored.

TABLE

Case	*Age (yr)*	*Sex*	*Weight (kg)*	*Type of Surgery*
1	22	F	76	Arthroscopy
2	25	F	82	Laparoscopic Cholecystectomy
3	30	M	80	Left Inguinal Herniorrhaphy
4	28	M	75	Arthroscopy
5	30	M	70	Right Inguinal Herniorrhaphy

Results

The T4/T1 ratio prior to cisatracurium administration was 1.0 in the control non-myasthenic patients, as well as in the myasthenic patient. However, the onset of neuromuscular block following 0.05 mg·kg^{-1} cisatracurium was more rapid in the myasthenic patient (3 min), than in the non-myasthenic patients (6.2 ± 0.8 min). Also, this dose of cisatracurium resulted in almost complete (97-98%) neuromuscular block in the myasthenic patient, while only 80-90% neuromuscular block was achieved in the non-myasthenic patients (Figure 1). Maintenance doses of 0.015 mg·kg^{-1} cisatracurium were required to maintain T4/T1 ratio of 0.25 at intervals of 20-30 min in the myasthenic patient, as compared with 17 ± 2.3 min in the non-myasthenic patients.

Reversal of neuromuscular block by neostigmine at the end of surgery was attempted in the non-myasthenic patients, when T4/T1 was less than 0.4; T4/T1 ratio of 0.75 was achieved within 10 min. In contrast, the administration of neostigmine in the myasthenic patient at T4/T1 ratio of 0.4 did not produce enhancement of the rate of recovery of neuromuscular transmission, despite repeating the dose of neostigmine after 10 min; a T4/T1 ratio of 0.75 was achieved 30 min after the first dose of neostigmine (Figure 2).

Following recovery of neuromuscular transmission, N_2O was discontinued, and the patient became conscious, resumed adequate spontaneous respiration, and the trachea was extubated. The myasthenic patient resumed his preoperative regimen of pyridostigmine on the day of operation, as soon as he could swallow. The pathology of the excised specimen showed hyperplasia of the thymus.

Discussion

Myasthenia gravis is the prototype of antibody-mediated autoimmune disease.[6] The role of the thymus gland is suggested by the association of myasthenia gravis with thymus gland abnormalities.[10] Electron microscopic studies of the neuromuscular junction in myasthenia gravis show that the postsynaptic membrane has abnormally sparse, shallow folds with markedly simplified geometric patterns.[11,12] The acetylcholine receptor antibodies accelerate degradation of the postsynaptic acetylcholine receptors of skeletal muscles, and receptor blockade may also be involved.[8] These degenerative processes at the postsynaptic membrane are associated with the loss of 70-89% of the functional acetylcholine receptors.[13] The decrease in available acetylcholine receptors results in a limited "safety margin", which explains the resistance of the myasthenic patient to succinylcholine,[14] and the paradoxical sensitivity to non-depolarizing relaxants.[6]

The present report suggests that this myasthenic patient was more sensitive to cisatracurium than were the non-myasthenic patients. The administration of 0.05 mg·kg^{-1} cisatracurium, equivalent to 1 x ED_{95} in normal patients, induced a rapid onset of a nearly complete neuromuscular block in the myasthenic patient and a slower onset of partial block in the control non-mysthenic patients. The rapid onset of marked nondepolarizing block in the myasthenic patient may be attributed to the decreased number of functional endplate acetylcholine receptors, with a consequent decrease of the safety margin of neuromuscular transmission.[15]

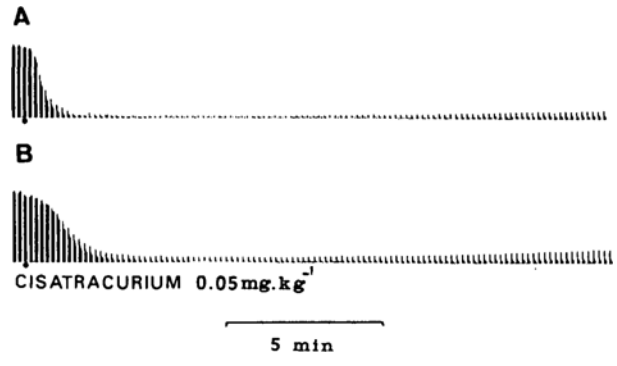

FIGURE 1 Train-of-four recordings, showing the effect of 0.05 mg·kg^{-1} cisatracurium on the onset and degree of maximal neuromuscular blockade in the myasthenic patient (A) *vs* one of the five non-myasthenic patients (B).

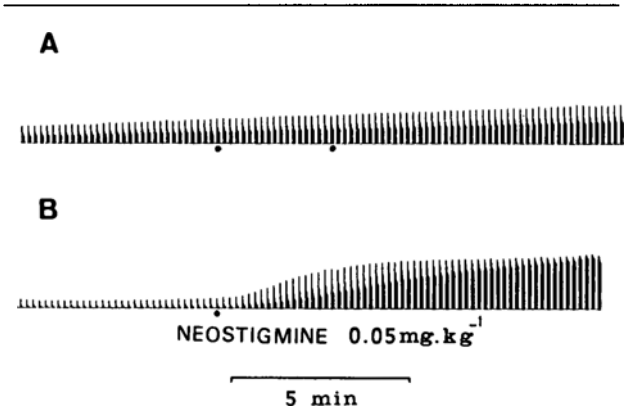

FIGURE 2 Train-of-four recordings, showing the rate of recovery from neuromuscular block after administration of two doses of 0.05 mg·kg^{-1} neostigmine(•) in the myasthenic (A) *vs* a single dose of neostigmine (•) in one of the five non-myasthenic patients (B).
• = Neostigmine 0.05 mg·kg^{-1} administered

It is controversial whether preoperative anticholinesterase therapy should be maintained or discontinued in the myasthenic patients scheduled for surgery. Patients who have only mild symptoms can interrupt their regimen, especially if the operative procedure is to take place early in the day.[16] In contrast, patients who are dependent on anticholinesterase therapy for their well-being and who have more than ocular symptoms, similar to our patient, would be best treated with little break in their usual anticholinesterase regimen.[16] Inhibition of acetylcholinesterase by the preoperative pyridostigmine may decrease the sensitivity to nondepolarizing muscle relaxants,[6] as observed with cisatracurium in our myasthenic patient, in whom maintenance requirements of cisatracurium were within the range seen in the non-myasthenic patients. A similar decreased sensitivity has been previously reported when vecuronium is used in myasthenic patients treated preoperatively with pyridostigmine therapy.[17]

Preoperative anticholinesterase therapy may also decrease the effectiveness of reversal of nondepolarizing neuromuscular block by neostigmine at the end of surgery. Previous experiments on the isolated phrenic nerve-diaphragm preparation of non-myasthenic rats have shown that the previous administration of an anticholinesterase results in an increase of the dose of nondepolarizing relaxants necessary to produce complete neuromuscular block, and renders subsequent reversal of the block by neostigmine ineffective.[18] In our myasthenic patient, neostigmine administration did not enhance the rate of recovery from cisatracurium neuromuscular block. This may be attributed to the inhibiton of acetylcholinesterase by the preoeprative pyridostigmine, as well as to possible desensitization of the endplate receptors secondary to the prolonged pyridostigmine therapy.

In conclusion, the present report investigated by electromyography the neuromuscular effects of cisatracurium in a myasthenic patient, compared with a control group of five non-myasthenic patients. In the myasthenic patient, 0.05 $mg \cdot kg^{-1}$ cisatracurium resulted in a rapid onset of complete neuromuscular block, while a slower onset of partial block was achieved in the control group. However, the maintenance dose requirements in the myasthenic patient were within the normal range. Preoperative anticholinesterase therapy may decrease the sensitivity of the myasthenic patient to cisatracurium, but it may also decrease the reversal effect of neostigmine at the end of surgery.

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