OPIS PRZYPADKU/CASE REPORT
Wpłynęło/Submitted: 03.05.2009 • Poprawiono/Corrected: 20.05.2009 • Zaakceptowano/Accepted: 22.05.2009

Variability of cisatracurium in myasthenia gravis: case report

José Ramón Ortiz-Gómez[1], Inocencia Fornet[2], Francisco J. Palacio[3]
[1] Department of Anesthesiology, Hospital Virgen del Camino, Pamplona, Spain
[2] Department of Anesthesiology, Hospital Puerta De Hierro, Madrid, Spain
[3] Department of Anesthesiology, Hospital Gregorio Marañón, Madrid, Spain

Summary

Case report. A myasthenic patient (Osserman II B), who received 0.1 mg.kg-1 cisatracurium during a propofol-fentanyl-O2:air anaesthesia, was monitored by Datex electromyography. The cisatracurium resulted in rapid onset of complete (100%) neuromuscular block in 3.6 min; a clinical duration (time from injection of cisatracurium to 25% ratio of the first twitch of the train-of-four to the control twitch (T1/C ratio)) of 42 min; a recovery index (25% to 75% T1/C ratio) of 37 min, and recovery TOF-ratios (ratio of the fourth to the first evoked response) of 0.75, 0.90, 0.95 and 1 in 65.5 min, 75.3 min, 84 min and 96.3 min respectively. ***Conclusion.*** The myasthenic patient is sensitive to cisatracurium, as evidenced by a more rapid onset and more marked neuromuscular block. This may be attributed to the decreased number of functional endplate acetylcholine receptors with a consequent decrease of the safety margin of neuromuscular transmission. *Anestezjologia i Ratownictwo 2009; 3: 123-127.*

Keywords: cisatracurium, myasthenia gravis, neuromuscular blockade

Introduction

Myasthenia gravis (MG) is a relatively common neuromuscular disease, with an incidence of about one in every 20 000 adults. The major characteristics of MG are weakness and rapid fatigability of voluntary skeletal muscles with repetitive use, followed by partial recovery with rest [1].

Case report

We describe a 47-year-old female patient, 58 kg, 160 cm, ASA 3 diagnosed previously with MG (Osserman and Genkins II B) [2], programmed for pleuropericardial metastatic resection of a malignant thymoma (approach by left thoracotomy). The patient presented bilateral palpebral ptosis with diplopia and positive test for fatigue. She was under p.o. treatment with pyridostigmine (240 mg per day), azathioprine (100 mg per day), prednisone (30 mg per 2 days) and omeprazol (20 mg per day).

Pre-operatively, the patient received her usual morning dose (60 mg) of pyridostigmine. She was monitored in the operating room with continuous electrocardiography, pulse oximetry and non-invasive arterial pressure. Electromyography (Datex Relaxograph) was used to monitor neuromuscular transmission. 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 (TOF-ratio), as well as the ratio of the first twitch of the train-of-four to the control twitch (T1/C ratio).

The anaesthetic induction was realised with fentanyl (0.15 mg) and propofol (150 mg). Following induction of anaesthesia, and while the patient was breathing

100% oxygen, the electromyographic response was recorded. When a steady twitch response was achieved, 0.1 mg.kg^{-1} cisatracurium (2 x ED_{95}) iv was injected. The time from the end of injection of the cisatracurium until maximum neuromuscular block (onset time), as well as the degree of maximum block, were both recorded. The trachea was intubated at the time of maximum block, and anaesthesia was maintained by Air: 0_2 mixture (2:1), propofol (continuous i.v. infusion) and supplemental doses of fentanyl.

Once intubated the patient was monitored with capnography, invasive arterial pressure, central venous pressure, diuresis and esophageal temperature. Hypothermia was prevented with fluid therapy warming and a hot air blanket.

The intervention lasted for 4.5 hours, and after uneventful extubation in the operating room, the patient was transferred to the Critical Care Unit, with adequate spontaneous ventilation and pulse oximetre values of 100% with an oxygen facial mask (inspiratory fraction of O_2 at 31%). There were no problems in the immediate postoperative period.

In this case, the cisatracurium induced neuromuscular block and showed rapid onset with complete block in 3.6 min (100% abolition of the TOF responses), a clinical duration (time from injection of cisatracurium to 25% T1/C ratio) of 42 min, a recovery index (time between 25% to 75% T1/C ratio) of 37 min, and times to recovery TOF-ratio values of 0.75, 0.90, 0.95 and 1 in 65.5 min, 75.3 min, 84 min and 96.3 min respectively.

Discussion

It is very important to know the pathophysiology of MG to understand its anaesthetic implications. MG is the prototype of autoimmune disease, resulting from the production of antibodies against the acetylcholine (Ach) receptors (AChRs) of the neuromuscular endplate synapse. AchR antibodies are detected in the sera of 85-90% of myasthenic patients (antibody-negative patients are usually those with mild or localised myasthenia). These antibodies generally belong to the IgG class, and reduce the number of active receptors, brought about either by functional partial block of the receptors, by increased rate of receptor degradation, or by complement-mediated lysis. However, it is not yet known what triggers the autoimmune response or what permits it to be sustained, although immunoregulatory defects and genetic predisposition have been postulated [3].

The immunoregulatory T cells play a key role in the pathogenesis of MG, possibly due to the sensitisation of T cells against the myoid AChRs when they are present in the thymus at a critical stage of maturation. The macrophage-associated AChRs interact with AChR-helper T cells, which proliferate and produce factors that promote anti-AChR antibody production from B cells.

Most of the antibodies bind to the main immunogenic region of the alpha subunit of the endplate receptors, with a direct effect on both sub-populations of AChRs: the stable AChRs (estimated to be about 80% of the total, with a half-life of over 12 days) and the rapidly turned-over (RTO) AChRs (the remaining 20%, which could be the precursors of the stable AChRs) [4]. The AChR antibodies may decrease the number of receptors, not only as a direct action against the stable receptors, but also by depletion of the RTOs. Thus, MG is largely a post-junctional disorder characterised by reduction of functional AChR. But, there could also exist a pre-junctional effect as autoantibodies may decrease presynaptic nicotinic autofacilitation, leading to a preferential decline of the neuromuscular response evoked at high stimulation rate, with less reduction of response at normal rates of stimulation.

The result in myasthenic muscles is that miniature endplate potential (MEPPP) frequency is normal, but the MEPP amplitude is decreased, and a large proportion of the endplate potentials are subthreshold. This is why repetitive nerve stimulation results in a decremental response [5].

MG may be associated with other disorders of autoimmune origin, and is characterised by bulbar and/or respiratory muscle weakness. Medical treatment of myasthenia gravis aims at improving neuromuscular transmission by anticholinesterases, suppressing the immune system with corticosteroids and immunosuppressants, or by decreasing the circulating antibodies by plasmapheresis. Thymectomy benefits nearly 96% of patients: 46% develop complete remission and 50% are asymptomatic or improve with therapy [3].

Preoperative preparation of MG patients is essential for the success of the surgery. Myasthenic patients may have little respiratory reserve, and hence depressant drugs for preoperative premedication should be used with caution and avoided in patients with bulbar symptoms. Anaesthetic management in MG must be

tailored according to the severity of the disease and the type of surgery required. In the case in question, we did not administer preoperative medication to the patient [6].

Myasthenic patients may be at increased risk of developing postoperative respiratory failure, especially in those with duration of MG for longer than six years, a previous history of chronic respiratory disease, pyridostigmine requirements greater than 750 mg per day, or preoperative vital capacity < 2.9 L (< 40 ml.kg^{-1}). These were not the circumstances in our patient, but the surgical approach (thoracotomy) recommends extreme precaution concerning the adequate recovery of neuromuscular function. The possibility of postoperative respiratory failure is the main criteria cited in preference of regional over general anaesthesia, especially with neuromuscular blocking drugs in MG. General anaesthesia can be performed safely when the patient is optimally prepared and neuromuscular transmission is adequately monitored during and after surgery. Adequate postoperative pain control, pulmonary hygiene, and avoidance of drugs that interfere with neuromuscular transmission are also key points to include [7,8].

In clinical use of neuromuscular blocking agents, it must be considered that the end-plate zone of myasthenic patients is less responsive than that of normal subjects to the excitatory action of ACh, and may be more readily desensitised by Ach [9], and so there is a subsequent decrease of the "safety margin" in the neuromuscular transmission. This is the main principle in understanding the response of MG to both depolarising and non-depolarising neuromuscular blocking agents, a necessary aspect for their safe administration. Myasthenic patients are sensitive to non-depolarising relaxants because the decrease of functional endplate receptors in MG can reduce the response to ACh, as well as to other depolarising agents such as suxamethonium. In contrast, this decreased "safety margin" results in a marked sensitivity to non-depolarising neuromuscular blocking agents [5].

It is also necessary to differentiate between MG and myasthenic syndrome (Lambert-Eaton syndrome), an acquired disorder of the motor nerve terminal in which quantal release of ACh is reduced. In contrast to MG patients, who are sensitive to non-depolarising muscle relaxants and resistant to depolarising relaxants, patients suffering from myasthenic syndrome are sensitive to both depolarising and non-depolarising relaxants.

It is not recommended to use suxamethonium in MG, because of its unpredictable response, even when associated with increased morbimortality, as described previously by Villani et al [10].

Intermediate-acting non-depolarising relaxants such as atracurium and vecuronium have been used in treatment of MG, and can be titrated to achieve the required neuromuscular block or even reversed at the end of surgery. Atracurium in MG patients shortened onset and prolonged recovery time, recovery index and total duration of block [11-13]. Compared with vecuronium in MG, some authors suggest that atracurium may have a lesser prejunctional effect [14] and a faster recovery index than vecuronium [15]. But other authors report lesser clinical duration for vecuronium (38 min to recover 25% of T1 amplitude after a single bolus of 0.04 mg.kg^{-1}) compared to atracurium (50 min to recover a 25% of T1 amplitude after a single bolus of 0.2 mg.kg^{-1}), despite the faster onset of atracurium (107 s) than with vecuronium (246 s) [16,17].

Mivacurium has also been used in MG [18,19]. In cumulative doses [20] after an initial bolus dose of 0.030 mg.kg^{-1} (approximately one-fifth of the normal intubating dose), a mean 37.5 % reduction in evoked twitch tension was observed. Neuromuscular block was increased with incremental doses and maintained with repeat bolus doses of 0.015 mg.kg^{-1} at 25% recovery. The interval between maintenance bolus doses remained constant (mean 5.9 min). Spontaneous offset was rapid with a mean recovery index of 11.9 min. The cumulative dose required to establish full neuromuscular block varied between 0.06 and 0.09 mg.kg-1. A maintenance infusion, commencing at 0.003 mg.kg^{-1}.min^{-1}, is recommended, guided by neuromuscular monitoring.

There is not a lot of experience with rocuronium [21,22], neither with cisatracurium in MG [23-25], although the same premises are fulfilled: deeper and faster onset and prolonged recovery of neuromuscular blockade with minor doses than in healthy patients (with a 2xED_{95} onset in 7 minutes, clinical duration in 45 min and clinical recovery index in 15 min).

It is also necessary to remark that the effect of other drugs such as sevoflurane can potentiate the neuromuscular block induced by cisatracurium [26] and the muscle monitored must not be affected. Therefore, the monitoring of the corrugator supercilii muscle can lead to abnormal interpretation of neuromuscular blockade [27].

In conclusion, this report suggests that the myasthenic patient was sensitive to cisatracurium, as evidenced by a more rapid onset and more marked neuromuscular block than normal 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. However, it is also necessary to obtain more cases for study.

Correspondence address:
José Ramón Ortiz Gómez
Hospital Virgen del Camino
Servicio de Anestesiología y Reanimación
C/ Irunlarrea 4. 31008 Pamplona, Navarra, Spain
Phone: 848429400
E-mail: jortizgo@cfnavarra.es

References

1. Drachman DB. Myasthenia gravis. N Engl J Med 1978; 298: 136-42.
2. Osserman KE, Genkins G. Studies on myasthenia gravis. Review of a twenty-year experience in over 1200 patients. M Sinai J M 1971; 38: 497-537.
3. Baraka A. Anaesthesia and myasthenia gravis. Can J Anaesth 1992; 39: 476-86.
4. Stanley EF, Drachman DB. Stabilization of acetylcholine receptors at neuromuscular junctions: analysis by specific antibodies. Ann N Y Acad Sci 1987: 505: 121-32.
5. Baraka A. Anesthesia and myasthenia gravis. Middle East J Anesthesiol 1993; 12: 9-35.
6. Cardone A, Congedo E, Aceto P, Sicuranza R, Chinè E, Caliandro F, De Cosmo G. Perioperative evaluation of myasthenia gravis. Ann Ital Chir 2007; 78: 359-65.
7. Santeularia MT, Unzueta MC, Casas JI, Vilanova F, Roldan J, Villar-Landeira J. Anestesia obstétrica en 15 mujeres con miastenia gravis. Rev Esp Anestesiol Reanim 1998; 45: 41-5.
8. De-Grazia R, Belluco A, Chiarini L, Nani R. Anesthesia with continuous infusion of propofol in myasthenic patients. Minerva Anestesiol 1992; 58: 101-4.
9. Grob D, Namba T. Characteristics and mechanism of neuromuscular block in myasthenia gravis. Ann N Y Acad Sci 1976; 274: 143-73.
10. Villani A, Primieri P, Adducci G, Mennella M, Lattanzi A, De-Cosmo G. Anesthesia in thymectomy. Experience with 115 cases. Minerva Anestesiol 1993; 59: 93-9.
11. Cortes C, Mora A, Mateo EM, Roige J, Cabarrocas E. Miastenia grave: timectomia. Relajacion muscular con besilato de atracurio. Rev Esp Anestesiol Reanim 1990; 37: 300-3.
12. Walz R, Lubbe N, Walz K, Mahr KH. Muscle relaxation with atracurium in myasthenia gravis. Anaesthesiol Reanim 1996; 21: 3-6.
13. Melloni C, Faenza S, Melotti R et al. Myasthenia and muscle relaxants. Minerva Anestesiol 1993; 59: 217-21.
14. Chan KH, Yang MW, Huang MH, Hseu SS, Chang CC, Lee TY, et al. A comparison between vecuronium and atracurium in myasthenia gravis. Acta Anaesthesiol Scand 1993; 37: 679-82.
15. Buzello W, Noeldge G, Krieg N, Brobmann GF. Vecuronium for muscle relaxation in patients with myasthenia gravis. Anesthesiology 1986; 64: 507-9.
16. Baraka A, Taha S, Yazbeck V, Rizkallah P. Vecuronium block in the myasthenic patient. Influence of anticholinesterase therapy. Anaesthesia 1993; 48: 588-90.
17. Baraka A, Tabboush Z. Neuromuscular response to succinylcholine-vecuronium sequence in three myasthenic patients undergoing thymectomy. Anesth Analg 1991; 72: 827-30.
18. Stillwell R, Mangar D, Turnage WS. Isoflurane and mivacurium chloride neuromuscular blockade in patients with myasthenia gravis. Nurse Anesth 1993; 4: 193-7.
19. Seigne RD, Scott RP. Mivacurium chloride and myasthenia gravis. Br J Anaesth 1994; 72: 468-9.
20. Paterson IG, Hood JR, Russell SH, Weston MD, Hirsch NP. Mivacurium in the myasthenic patient. Br J Anaesth 1994; 73: 494-8.
21. Baraka A, Haroun-Bizri S, Kawas N, Hajjar AM, Kawkabani N. Rocuronium in the myasthenic patient. Anaesthesia 1995; 50: 1007.
22. Sanfilippo M, Fierro G, Cavalletti MV, Biancari F, Vilardi V. Rocuronium in two myasthenic patients undergoing thymectomy. Acta Anaesthesiol Scand 1997; 41: 1365-6.
23. Rama-Maceiras P, Bonome C, Davila M. Uso del cisatracurio en un caso con miastenia gravis. Rev Esp Anestesiol Reanim 1998; 45: 442-3.
24. Haroun-Bizri S, Maalouli J, Deeb P, Baraka A. Anesthetic management for a patient with myasthenia gravis undergoing coronary artery bypass graft. Middle East J Anesthesiol 2003; 17: 299-305.

25. Baraka A, Siddik S, Kawkabani N. Cisatracurium in a myasthenic patient undergoing thymectomy. Can J Anaesth 1999; 46: 779-82.
26. Baraka AS, Taha SK, Kawkabani NI. Neuromuscular interaction of sevoflurane--cisatracurium in a myasthenic patient. Can J Anaesth 2000; 47: 562-5.
27. Devys JM, Guellec V, Corré A, Plaud B. Neuromuscular blockade monitoring at the corrugator supercilii and ocular myasthenia gravis. Ann Fr Anesth Reanim 2003; 22: 242-4.