Variability of cisatracurium in myasthenia gravis: case report

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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 2 Hz, 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: O\(_2\) 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 depresant 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, pyri-
dostigmine 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 posto-
perative 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, pulmo-

nary 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 myaste-
nic 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 depola-
rising 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 suxame-
thonium. 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 rel-
xants, 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 atra-
curium may have a lesser prejunctural 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 recom-

mended, 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 2xED₉₀ 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 supercili 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.

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