Anesthetic Implications of Myasthenia Gravis

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Abstract

Myasthenia gravis is a disease of great significance to the anesthesiologist, because it affects the neuromuscular junction. Many patients with this condition are treated by surgical thymectomy, using techniques developed by Mount Sinai physicians, including Dr. Paul Kirschner, Dr. Alan E. Kark, and the late Dr. Angelos E. Papatestas. The authors review the anesthetic considerations in the management of patients with myasthenia gravis who are undergoing thymectomy and other surgical procedures.

Key Words: Myasthenia gravis, anesthesia, thymectomy.

Epidemiology and Pathophysiology

MYASTHENIA GRAVIS (MG) is an autoimmune disease characterized by weakness and fatigability of skeletal muscles, with improvement following rest. It may be localized to specific muscle groups or it may be generalized. The incidence is 50–142 cases per million population (1). MG is caused by a decrease in the numbers of postsynaptic acetylcholine receptors at the neuromuscular junction (2), which decreases the capacity of the neuromuscular end-plate to transmit the nerve signal. Initially, in response to a stimulus resulting in depolarization, acetylcholine is released presynaptically. In MG, the number of activated postsynaptic receptors may be insufficient to trigger a muscle action potential (3). Further, with repeated stimulation, the decline in release of acetylcholine correlates with the characteristic fatigability (4).

Presentation and Diagnosis

The characteristic presentation of MG is fatigability of voluntary muscles. Most commonly, the eyelids and extraocular muscles are involved. Bulbar involvement may be manifested as difficulty in chewing and swallowing. Eighty-five percent of myasthenic patients go on to develop generalized weakness; some develop respiratory failure. Thymoma is present in 10–15% of patients with MG (5). In a now classic paper, Osserman and Genkins, both physicians at The Mount Sinai Hospital, published a clinical classification of myasthenia gravis that is still in widespread use (6).

The diagnosis of MG can be confirmed by several tests. The anticholinesterase test is positive if strength improves with inhibition of cholinesterase. When cholinesterase is inhibited, more acetylcholine is available to interact with the decreased number of postsynaptic receptors, increasing the likelihood of adequate end-plate depolarization. Edrophonium (Tensilon®) is usually administered intravenously in small (2–8 mg) doses for this test. This test was introduced and popularized by Dr. Osserman (7). Electromyography is also used in the diagnosis of myasthenia. Repetitive stimulation of a peripheral motor nerve leads to decreasing responses by the innervated muscle in a patient with MG. The presence of anti-acetylcholine antibodies in the serum, as detected by radioimmunoassay, is diagnostic of MG. Such antibodies may not be detectable, however, in all patients with mild symptoms at presentation.

Treatment

Treatment of MG may be medical or surgical, utilizing one of three approaches: anticholinesterases (medical), immune suppression (medical), or thymectomy (surgical).

Improving neuromuscular transmission by means of anticholinesterase agents is the most common approach. Pyridostigmine (Mestinon) in a dose of up to 120 mg p.o. every 3 hours is
used because it is tolerated well orally, with few muscarinic side effects, and has a relatively long duration of action. Pyridostigmine 30 mg orally is equivalent to 1 mg intravenously or intramuscularly.

Immune suppression is directed at preventing or attenuating the destruction of acetylcholine receptors at the motor end plate (8). Corticosteroids, which cause immune suppression, will improve the condition of most myasthenics (9). Those who do not respond or who cannot tolerate the side effects may respond to azathioprine 2.5–3.5 mg/kg. Cyclosporine has been used in patients with MG (10) and compares favorably with azathioprine (11).

For patients with severe bulbar symptoms or respiratory compromise (myasthenic crisis), plasmapheresis is used (12). Significant improvement occurs over days, with decreased dependence on ventilatory support (13). The presumed mechanism is the removal of antibodies, allowing receptors to proliferate. Immune globulin given intravenously has been used to treat myasthenic crises when plasmapheresis cannot be used. Its use has been associated with good short-term improvement (14).

Thymectomy is used to treat MG, but the mechanism of its action remains speculative. Antibody titers decrease with clinical improvement (15). Suggested mechanisms include removal of antigenic stimulus by the removal of myoid cells or alterations in immune regulation by removal of the thymus. For an up-to-date history of surgery of the thymus gland, as well as speculation on the future, the recent review by Kirschner (16) is recommended reading.

Anesthesia Considerations — Preoperative Evaluation and Preparation

Preoperative evaluation of the MG patient includes review of the severity of the patient’s disease and the treatment regimen. Specific attention should be paid to voluntary and respiratory muscle strength. The patient’s ability to protect and maintain a patent airway postoperatively may be compromised if any bulbar involvement exists preoperatively. The ability to cough and clear secretions may be compromised as well. Respiratory muscle strength can be quantified by pulmonary function tests (negative inspiratory pressure and forced vital capacity). These tests may be necessary as a reference to determine the optimal conditions for extubation postoperatively as well as the need for postoperative mechanical ventilation (17, 18).

If a thymoma presents an anterior mediastinal mass, intrathoracic airway or vascular obstruction may occur upon the induction of anesthesia. Flow-volume loops may be indicated preoperatively. Maximal inspiratory and expiratory flow-volume loops obtained with the patient in the supine and upright positions will measure the extent of the respiratory impairment as well as whether the impairment is fixed or dynamic.

The preoperative management of the myasthenic patient will be influenced by the surgical procedure and the preferences of the surgeon and the anesthesiologist. Some choose to omit anticholinesterase on the morning of surgery, to decrease the need for muscle relaxants (21), whereas others continue its use for psychological support of the patient. If the patient is poorly controlled, a course of plasmapheresis may be of benefit in the preoperative period (22). The steroid-dependent patient will require perioperative coverage.

Anxiolytic, sedative, and opioid premedications are rarely given to patients who may have little respiratory reserve. If the patient has primarily ocular symptoms, a small dose of benzodiazepine is acceptable.

Response to Anesthetic Drugs

Nondepolarizing Neuromuscular Blockers

Neuromuscular blocking drugs act by interrupting neuromuscular transmission at the level of the nicotinic acetylcholine receptors at the motor end plate. Their mode of action can be classified as antagonist (nondepolarizing) or agonist (depolarizing), both producing blockade (23). The myasthenic patient is typically sensitive to nondepolarizing neuromuscular blockers. The use of a small dose for priming or defasciculation is not appropriate, because it may result in loss of airway protection or in respiratory distress. Sensitivity to nondepolarizing agents has been described in patients with minimal disease (i.e., ocular symptoms only) (24), in those in apparent remission (25), or those with subclinical undiagnosed myasthenia (26).

Long-acting muscle relaxants such as d-tubocurarine, pancuronium, pipecuronium, and doxacurium, are best avoided in these patients. Intermediate and short-acting nondepolarizing agents can be used with careful monitoring of neuromuscular transmission, preferably with electromyogram (EMG) or mechanomyogram...
(MMG), which measure the evoked electrical or mechanical responses following electrical stimulation of a peripheral motor nerve. Stimuli can be delivered singly (0.1 Hz or one every 10 seconds; 1 Hz or one per second), or in trains-of-four (TOF) stimuli (2 Hz) at 10-second intervals. In the absence of a neuromuscular block, a control response is obtained. This control “twitch” is designated Tc. In the absence of a neuromuscular block, all responses should be of equal magnitude. Thus, with TOF stimulation, the control, first, second, third and fourth responses are equal (Tc=T1=T2=T3=T4). In the presence of a nondepolarizing block, Tc>T1 and T4<T3<T2<T1. The ratio of T4 /T1 is called the fade ratio and is used to assess the extent of a nondepolarizing block. In the presence of a depolarizing or phase I block (due to succinylcholine) Tc>T1 but T1=T4, i.e., there is no fade with this type of block. Sometimes a phase I block changes in nature and takes on the characteristics of a nondepolarizing block (i.e., fade develops). The latter block is called a phase II block.

In myasthenic patients, the ED95 for vecuronium ranges from 40% (17 µg/kg vs. 24 µg/kg) (27) to 55% (20 µg/kg vs. 36 µg/kg) (28) of that in normal controls. There are wide variations in responses among myasthenics. Elimination of vecuronium is not altered. Wide variability in requirements was also noted for atracurium (29). The ED95 was 58% (0.14 mg/kg vs. 0.24 mg/kg) of the value for normal patients (30). Myasthenic patients are similarly sensitive to cisatracurium, as evidenced by a more rapid onset and more marked neuromuscular block compared with control patients (31).

Increased sensitivity to mivacurium has also been reported (32). Recovery was prolonged (recovery index 25–75% for T1 of 20.5 minutes vs. 11.9 minutes) in a patient receiving pyridostigmine (33). Pyridostigmine inhibits the metabolism of mivacurium and therefore increases recovery times when mivacurium is administered. It should therefore be used with caution in patients receiving pyridostigmine on the morning of surgery.

**Depolarizing Neuromuscular Blocker**

**(Succinylcholine)**

Patients with MG show resistance to depolarizing agents (34–36). It is probable that the requirements are increased due to the loss of receptors, because these agents create neuromuscular block by agonist action. The ED95 of succinylcholine in MG patients is 2.6 times that in non-myasthenic patients (0.8 mg/kg vs. 0.3 mg/kg) (34). The dose of succinylcholine used for rapid airway control in normal patients, 1.5 mg/kg, is approximately five times the ED95 in MG. A dose of 1.5–2.0 mg/kg should be adequate for most myasthenics, for rapid sequence intubation (34). A case report of a myasthenic patient in complete remission showed a normal sensitivity to succinylcholine (37). Myasthenic patients are more likely than normal patients to develop a phase II block, particularly with repeated doses of succinylcholine (38). Cholinesterase depletion due to plasmapheresis (39) or inhibition caused by pyridostigmine given preoperatively may affect the metabolism of succinylcholine (40) and mivacurium (32), resulting in prolonged blockade.

**Potent Inhaled Anesthetic Agents**

Inhaled anesthetics may cause muscle relaxation in normal patients (41). This effect may be profound. Isoflurane depresses T1 and increases train-of-four fade in the myasthenic patient (42). It produces twice as much twitch height depression as equipotent concentrations of halothane (43). There may be some variability in the response among myasthenics (41, 44). Train-of-four responses are also decreased to varying degrees in myasthenic patients receiving enflurane (45, 46).

Sevoflurane at 2.5% — slightly greater than 1 MAC (minimum alveolar concentration) — depresses (EMG) responses, with T1/Tc at 47% and T4/T1 at 57% (47). A recent report found sevoflurane was suitable as a sole anesthetic for a myasthenic undergoing sternal split thymectomy, implying that sevoflurane alone provided adequate muscle relaxation (48). Sevoflurane appears to depress neuromuscular transmission to the same degree as isoflurane, although in one myasthenic patient the sensitivity was much greater (>85% T1 suppression) (49). TOF stimulation in most patients anesthetized with halothane revealed measured decrements in evoked responses (50).

Although to date no work has been reported on the effects of desflurane in myasthenics, in normal patients the requirements for muscle relaxants are decreased in the presence of desflurane (51, 52). It is likely that in myasthenic patients desflurane will have the same effect as the other potent, inhaled, volatile anesthetic agents discussed above.
Intravenous Anesthetic Agents

Anesthetic management using barbiturates and propofol for myasthenic patients without untoward effects have been described (53, 54). Propofol has the theoretic advantages of short duration of action without effect on neuromuscular transmission.

Opioid analgesics in therapeutic concentrations do not appear to depress neuromuscular transmission in myasthenic muscle (55, 56). However, central respiratory depression may be a problem with opioids. The introduction of short-acting opioids makes these drugs more titratable in the myasthenic. Remifentanil’s short elimination half-life (9.5 minutes) (57) makes the drug appealing. To date, there are no reports of its use in MG. There are reports of uneventful anesthesia using etomidate (58), althesin (58) and ketamine in myasthenic patients (59).

Interactions with Other Drugs

Many commonly used drugs affect neuromuscular transmission to a small degree. In normal patients, this is usually of no clinical significance. In the myasthenic patient, upon emergence from anesthesia and surgery, the interactions of these drugs with residual anesthetic effect and the disease state of MG may be more significant.

The most commonly used drugs known to depress neuromuscular transmission are the aminoglycoside antibiotics and the polymyxins (60–62). Beta adrenergic blockers, regardless of their mode of administration, have been shown to exacerbate MG (63, 64).

Corticosteroids, although used in the treatment of MG, may also exacerbate MG (62). Corticosteroids have not been shown to affect the dose-response to succinylcholine, but they have been shown to decrease the dose requirements for nondepolarizing relaxants in myasthenics (65). Procainamide was reported to cause weakness in a myasthenic patient (66). Phenytoin has caused clinical weakness in a myasthenic patient (67); however, it has been used without clinical side effects for seizure disorders in patients with MG (68).

Regional Anesthesia

Potentiation of neuromuscular blocking drugs by local anesthetics has been reported (69, 70). These agents decrease the sensitivity of the postjunctional membrane to acetylcholine (71). This theoretically could cause weakness in myasthenics if blood levels are high enough. Ester anesthetics, which are metabolized by cholinesterase, may present particular problems in patients taking anticholinesterases. Regional and local anesthesia should be performed using reduced doses of amide (rather than ester) local anesthetics to avoid high blood levels. Traditionally, blockade of the innervation of intercostal muscles is avoided to minimize the risk of respiratory muscle weakness. Recently, however, the safe and successful use of thoracic epidural blockade with bupivacaine for intraoperative anesthesia and postoperative analgesia for transsternal thymectomy has been reported (72, 73). Spinal anesthesia has the advantage of reduced drug dosage, whereas epidural techniques facilitate easier control of blockade level and may obviate the need for opioids in postoperative pain management.

Anesthesia Management

The safe use of general anesthesia requires attention to monitoring the patient and understanding the variable responses that the myasthenic may have to many drugs. The EMG and the mechanomyograph are the preferred methods for monitoring neuromuscular transmission. They record control values to compare with those elicited throughout surgery and postoperatively. Recently, submaximal train-of-four stimulation in awake patients has been advocated (74). Similarly, the presence of fade (T4/T1 < 0.9) in the preanesthetic period predicts decreased atracurium requirements in patients with MG (75). This technique, along with preoperative pulmonary function testing (17), may be useful in determining preoperative baseline function.

Several general anesthetic techniques have been proposed, although none has been proven to be superior to the others. Some prefer to avoid muscle relaxants altogether and use potent inhaled agents both for facilitating tracheal intubation and providing relaxation for surgery. These agents allow neuromuscular transmission to recover, with rapid elimination of these agents at the end of surgery. In theory, desflurane and sevoflurane may offer some advantages, due to their low blood solubility. Sevoflurane is probably superior to desflurane, due to its lower incidence of excitatory airway reflexes during inhalational induction. Others
titrate small doses (10–25% of the ED<sub>95</sub>) of intermediate-acting relaxants to the evoked MMG or EMG for both intubation and surgical relaxation, if required. The decision as to whether to reverse residual neuromuscular blockade at the end of surgery is controversial. Some argue that the presence of anticholinesterases and antimuscarinics will confuse efforts to differentiate weakness due to inadequate neuromuscular transmission from cholinergic crisis in the recovery room. They prefer spontaneous recovery and extubation when the patient has demonstrated adequate parameters for extubation (i.e., head-lift, tongue protrusion).

Total intravenous anesthesia (TIVA) for the management of myasthenics has been reported (53). In the authors’ experience, hemodynamic instability in older patients makes this approach difficult, whereas younger patients usually tolerate it without difficulty. The use of remifentanil as part of TIVA may alleviate some of the hemodynamic instability.

When possible, many clinicians prefer to utilize regional or local anesthetic techniques. Regional techniques may reduce or eliminate the need for muscle relaxants in abdominal surgery. Epidural techniques offer the advantage of postoperative pain control with minimal or no opioid use.

Postoperative Considerations

There have been several attempts to predict the need for postoperative ventilation (17, 76, 77). Based on the preoperative condition of the patient, the surgical procedure, and the residual anesthetic effects, a carefully planned extubation may be carried out in most patients. Adequate postoperative pain control, pulmonary toilet, and the avoidance of drugs that interfere with neuromuscular transmission will facilitate tracheal extubation. All patients with MG should be closely monitored postoperatively in the postanesthesia care unit or the surgical intensive care unit, where respiratory support can be immediately re instituted. Weakness after surgery presents a special problem in MG patients. The differential diagnosis includes myasthenic crisis, residual effects of anesthetic drugs, nonanesthetic drugs interfering with neuromuscular transmission and cholinergic crisis.

Cholinergic Crisis

Cholinergic crisis results from an excess of acetylcholine at the nicotinic and muscarinic recep
tors. It usually results from administration of excess anticholinesterase drugs. Nicotinic overstimulation results in involuntary twitching, fasciculations, and weakness (sometimes leading to respiratory arrest). The weakness results from an inability to coordinate muscle contraction and relaxation. When the muscarinic effects are obvious, the diagnosis is easily made. Antimuscarinics and respiratory support are indicated. When acetylcholinesterase inhibition in conjunction with antimuscarinics has been used to reverse residual neuromuscular blockade, weakness and fasciculations may predominate in the absence of muscarinic symptoms. To differentiate this from myasthenic crisis, an edrophonium (Tensilon<sup>®</sup>) test may be administered. Also, in a myasthenic crisis, the pupils will be dilated. In the absence of muscarinic symptoms, simply allowing the patient to recover clinically, without elaborate testing, while maintaining mechanical respiratory support, constitutes a safe and practical approach. For these reasons, many clinicians prefer to avoid the use of muscle relaxants, or if they do so, to allow the neuromuscular block to recover spontaneously, avoiding the use of anticholinesterase in the immediate postoperative period.

Conclusions

Myasthenia gravis is a disease with many implications for the safe administration of anesthesia. The potential for respiratory compromise in these patients requires the anesthesiologist to be familiar with the underlying disease state, as well as the interaction of anesthetic and nonanesthetic drugs with MG. Thymectomy is a surgical procedure commonly undergone by patients with MG.

References


