THE MYASTHENIC SYNDROME: ANAESTHESIA IN A PATIENT TREATED WITH 3.4 DIAMINOPYRIDINE

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SUMMARY

A case of anaesthesia in a patient with myasthenic syndrome treated with 3.4 diamino-pyridine is described. Despite symptomatic improvement and an improved electromyogram (EMG) on treatment, extreme sensitivity to neuromuscular block occurred with vecuronium. Antagonism of block was poor with an anticholinesterase, while oral 3.4 diaminopyridine improved neuromuscular transmission further. A combination of anticholinesterase with aminopyridine may be the antagonistic combination of choice in this condition.

KEY WORDS

Myasthenic syndrome: 3.4 diaminopyridine.

The myasthenic syndrome (Eaton Lambert Syndrome) is a rare disorder of neuromuscular transmission resembling myasthenia gravis [1]. It is a syndrome of muscle weakness, originally described in association with malignant disease, classically small cell bronchogenic carcinoma. It has been described subsequently in patients in whom no malignancy has been detected [2]. Muscle weakness is caused by diminished release of transmitter from motor nerve endings [3], secondary to morphological destruction of the active release zones in the nerve terminal [4]. It is thought to have an autoimmune aetiology [5]. Cholinesterase inhibitors, effective in the treatment of myasthenia gravis, do not produce significant improvement in most patients [3]. Recently, reports have been published of the successful use of aminopyridines (quaternary ammonium compounds that increase neurally evoked acetylcholine release) in the treatment of this disorder [6–8].

Reports of anaesthesia in patients with the myasthenic syndrome are rare. We describe a case of successful anaesthesia in a patient with the myasthenic syndrome, treated with oral 3.4 diaminopyridine.

CASE REPORT

A 67-yr-old retired compositor was scheduled for microscopic surgical removal of a prolapsed L5/S1 disc impinging on the S1 nerve root.

Pre-operative assessment revealed a history of small cell bronchogenic carcinoma, currently in remission following recent chemotherapy. Previous anaesthetic history included an uneventful general anaesthetic for mediastinoscopy 1 yr previously. Induction of anaesthesia had been with thiopentone 325 mg, followed by atracurium 35 mg i.v.; anaesthesia was maintained with 70% nitrous oxide and enflurane in oxygen. Thirty-five minutes later antagonism of neuromuscular block with glycopyrrolate 0.5 mg and neostigmine 2.5 mg i.v. was said to be uneventful. He was also noted to have moderate aortic stenosis, inappropriate secretion of antidiuretic hormone (sodium 123 mmol litre⁻¹, potassium 3.6 mmol litre⁻¹ and urea 3.5 mmol litre⁻¹), autonomic neuropathy (lack of beat-to-beat variation in heart rate, postural hypotension, arterial pressure decreasing from 140/60 mm Hg lying to 110/40 mm Hg standing) and myasthenic syndrome. The latter had been diagnosed 6 months earlier following the development of severe progressive leg weakness and treated with 3.4 diaminopyridine 20 mg 6-hourly by mouth.

Other investigations included blood-gas...
measurements (pH 7.4; \(P_{\text{aCO}_2}\) 4.2 kPa; \(P_{\text{aO}_2}\) 8.9 kPa; \(HCO_3^-\) 20.9 mmol litre\(^{-1}\); base excess -3 mmol litre\(^{-1}\)) and respiratory function tests (peak expiratory flow rate (PEFR) 400 litre min\(^{-1}\) forced expiratory volume in 1 s (FEV\(_1\) 2.0 litre; forced vital capacity (FVC) 2.8 litre; FEV\(_1\):FVC ratio 0.71). Predicted values were FEV\(_1\) 3 litre, FVC 4.3 litre, FEV\(_1\):FVC ratio 0.69. Haemoglobin was 12.5 g dl\(^{-1}\). Electrocardiography showed sinus rhythm with T wave inversion in leads, 1, V5 and V6.

The patient received his normal morning dose of 3.4 diaminopyridine 20 mg orally. Premedication was with papaveretum 10 mg and hyoscine 0.2 mg. On arrival of the patient in the anaesthetic room, an i.v. cannula and a radial artery cannula were inserted under local anaesthesia. Neuromuscular transmission monitoring commenced using a Datex Relaxograph. Electrodes were placed over the right ulnar nerve and hypothenar eminence. Calibration and baseline values were obtained. Anaesthesia was induced with papaveretum 10 mg and thiopentone 200 mg. Neuromuscular block was monitored by supramaximal train-of-four (TOF) stimulation every 20 s. Suxamethonium 50 mg was administered to facilitate tracheal intubation. Anaesthesia was maintained with 70% nitrous oxide and 0.5% isoflurane in oxygen. Ventilation was adjusted to maintain normocapnia (Datex Cardio-cap). Seven and a half minutes later, when the T1 twitch height has recovered to 50% of control, a bolus dose of vecuronium 1 mg was administered. This reduced T1 twitch height to 20%. Surgery was commenced. Four further increments of vecuronium 0.5 mg were administered to maintain T1 twitch height less than 20%. Surgery lasted 100 min. Offset of vecuronium was very slow. T1 twitch height recovered from 5% to 25% of control in about 40 min. One hour after the last increment of vecuronium, T1 twitch height was only 30% of control with a T4:T1 ratio of 0.42. Two minutes after antagonism with neostigmine 1.25 mg and glycopyrrolate 0.25 mg, T1 twitch height was 40% of control with a T4:T1 ratio 0.5. A further dose of neostigmine 1.25 mg and glycopyrrolate 0.25 mg improved T1 twitch height to 55% of control, with T4:T1 ratio 0.64. A third dose of neostigmine 2.5 mg and glycopyrrolate 0.5 mg produced little improvement in either T1 twitch height or T4:T1 ratio. At this stage isoflurane was discontinued. Ventilation was judged adequate. The patient was able to lift his head and open his eyes. The trachea was extubated and the patient returned to the recovery ward. Neuromuscular function monitoring was continued at 30-min intervals. No further improvement was demonstrable in T1 twitch height or T4:T1 ratio. However, 40 min after administration of 3.4 diaminopyridine 20 mg orally, T1 twitch height increased to 89% of control with a T4:T1 ratio of 0.7. This improvement was maintained for the next 3 h, after which neuromuscular function monitoring was discontinued.

**DISCUSSION**

The myasthenic syndrome is a rare disorder of neuromuscular transmission caused by diminished transmitter release from motor nerve endings secondary to autoimmune morphological destruction of active release zones of the nerve terminal. The dominant neurological features in a recent review of 50 cases [2] were proximal lower limb weakness (100%), depressed tendon reflexes (92%), autonomic features, especially dryness of the mouth (74%) and mild moderate ptosis (54%). If it is suspected clinically, diagnosis is made by the characteristic electromyographic criteria. The amplitude of the initial muscle action potential (APmusc) evoked by nerve stimulation is abnormally small and shows a decremental response at low rates of stimulation (1–3 Hz) with an incremental response on high frequency stimulation or after maximal voluntary contraction. There is no improvement with edrophonium (table I).

In contrast, myasthenia gravis is a disease of the neuromuscular junction caused by autoimmune destruction or inactivation of the acetylcholine receptors. The dominant neurological features are dependent on the skeletal muscle group affected. Ptosis and diplopia are the most common initial complaints. Skeletal muscle and bulbar weakness also are seen. Electromyographic testing reveals an APmusc of relatively normal amplitude with a decremental response on high frequency stimulation (fade). There is improvement with edrophonium (table I).

Treatment of the myasthenic syndrome is aimed at improving neuromuscular transmission. Cholinesterase inhibitors have not been found to be effective [3]. Guanidine, a compound that increases the release of acetylcholine from nerve terminals, has helped patients with this condition, but its use has been limited by serious side effects.
### Table I. Distinctions between myasthenia gravis and myasthenic syndrome. APmusc = Muscle action potential

<table>
<thead>
<tr>
<th></th>
<th>Myasthenia Gravis</th>
<th>Myasthenic Syndrome</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Female &gt; Male</td>
<td>Male &gt; Female</td>
</tr>
<tr>
<td><strong>Presenting symptoms</strong></td>
<td>External ocular muscle, bulbar and facial weakness</td>
<td>Proximal limb weakness, legs &gt; arms</td>
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<tr>
<td><strong>Other symptoms</strong></td>
<td>Fatigue on activity</td>
<td>Increased strength on activity precedes fatigue</td>
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<td><strong>EMG</strong></td>
<td>Initial APmusc relatively normal</td>
<td>Initial APmusc abnormally small</td>
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<td></td>
<td>Decremental response on high frequency stimulation (“fade”)</td>
<td>Decremental response at low rates of stimulation, incremental response on high frequency stimulation</td>
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<tr>
<td><strong>Response to blocking drugs</strong></td>
<td>Sensitivity to non-depolarizing blockers</td>
<td>Sensitivity to both non-depolarizing and depolarizing blockers</td>
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<tr>
<td></td>
<td>Resistance to depolarizing blockers</td>
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<td></td>
<td>Good response to anticholinesterases</td>
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<tr>
<td><strong>Pathological state</strong></td>
<td>Thymoma present in 20–25% of patients</td>
<td>Small cell bronchogenic carcinoma usually present</td>
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[9]. Recently, there has been an interest in the use of aminopyridines in the treatment of this condition. These compounds increase the release of acetylcholine at the neuromuscular junction [10]. The mechanism of action is selective block of potassium channels. As the rate of efflux of potassium determines the duration of the action potential, block of the potassium channels prolongs the action potential and allows more calcium to move into the cell. As the intracellular uptake of calcium is essential for release of acetylcholine, the increased influx following treatment with aminopyridine may result in increased release of acetylcholine [11]. 4 Aminopyridine has been tested as treatment for the myasthenic syndrome, but its usefulness is limited by central nervous system stimulant effects, sometimes causing seizures [6,7]. 3.4 Diaminopyridine has been shown in animal experiments to be more potent in improving neuromuscular transmission [12]. Clinically, it causes less central nervous stimulation and is less convulsant than 4 aminopyridine. It is probably the drug of choice in the treatment of this condition [8]. Treatment is usually commenced at a low dose which is increased and titrated against response. Maximum dosage is 100 mg daily, given orally in divided doses.

There are few reports of anaesthesia in patients with myasthenic syndrome. Wise, in 1962, originally described the extreme sensitivity of such patients to non-depolarizing neuromuscular blocking drugs [13]. He also showed enhanced sensitivity to depolarizing blockers despite normal plasma cholinesterase in three patients. The exquisite sensitivity of patients with myasthenic syndrome to tubocurarine was described also in an isolated arm technique [14]. We have not found previous reports of anaesthesia in a patient with myasthenic syndrome treated with 3.4 diaminopyridine. Our patient did not show an abnormal response to suxamethonium. Interestingly, serum analysis revealed a cholinesterase concentration of 62 u (normal range 80–120 u) with normal fluoride and dibucaine numbers and genotype E<sup>i</sup>, E<sup>j</sup>. The small reduction in cholinesterase activity can be attributed probably to the effects of recent chemotherapy [Cholinesterase Research Laboratory, Hammersmith Hospital, personal communication]. Despite symptomatic improvement and an improved EMG on treatment with 3.4 diaminopyridine, our patient was exquisitely sensitive to a non-depolarizing neuromuscular blocker. The T<sub>1</sub> 5% to 25% recovery time of 40 min compares with one of 7 min in normal patients following a single 0.1-mg kg<sup>−1</sup> dose of vecuronium [15]. Given the underlying pathology of the condition, it was not surprising that response to attempted antagonism of neuromuscular block with an anticholinesterase was poor. The further improvement in neuromuscular
transmission with 3.4 dianminopyridine is interesting. Unfortunately, this drug is available only as an oral preparation at present. 4 Aminopyridine is available as an i.v. preparation and has been advocated as an antagonist to non-depolarizing blockers in man. Its usefulness is limited because the doses required produce central nervous system excitation. However, small i.v. doses of 4 aminopyridine, which by themselves produce no antagonism of neuromuscular block, potentiate the effects of neostigmine and pyridostigmine when antagonizing pancuronium in man [16] and vecuronium in rats [17]. It would have been useful to have had this drug available for this particular patient.

In conclusion, we have described a case of anaesthesia in a patient with myasthenic syndrome treated with 3.4 dianminopyridine who showed a normal response to suxamethonium and marked sensitivity to vecuronium with extremely slow offset time. Antagonism of residual neuromuscular block with neostigmine was largely ineffective, but oral 3.4 dianminopyridine improved neuromuscular transmission further. If such a patient presents for anaesthesia, it would seem logical to continue 3.4 dianminopyridine up to the time of surgery. If possible, neuromuscular blockers should be avoided, but when necessary, they should be used sparingly and neuromuscular transmission should be monitored closely. If antagonism of neuromuscular block is required, a combination of an anticholinesterase and a small dose of i.v. 4 aminopyridine would seem to be the antagonizing combination of choice. Oral 3.4 dianminopyridine therapy should be recommenced as soon as possible.

REFERENCES